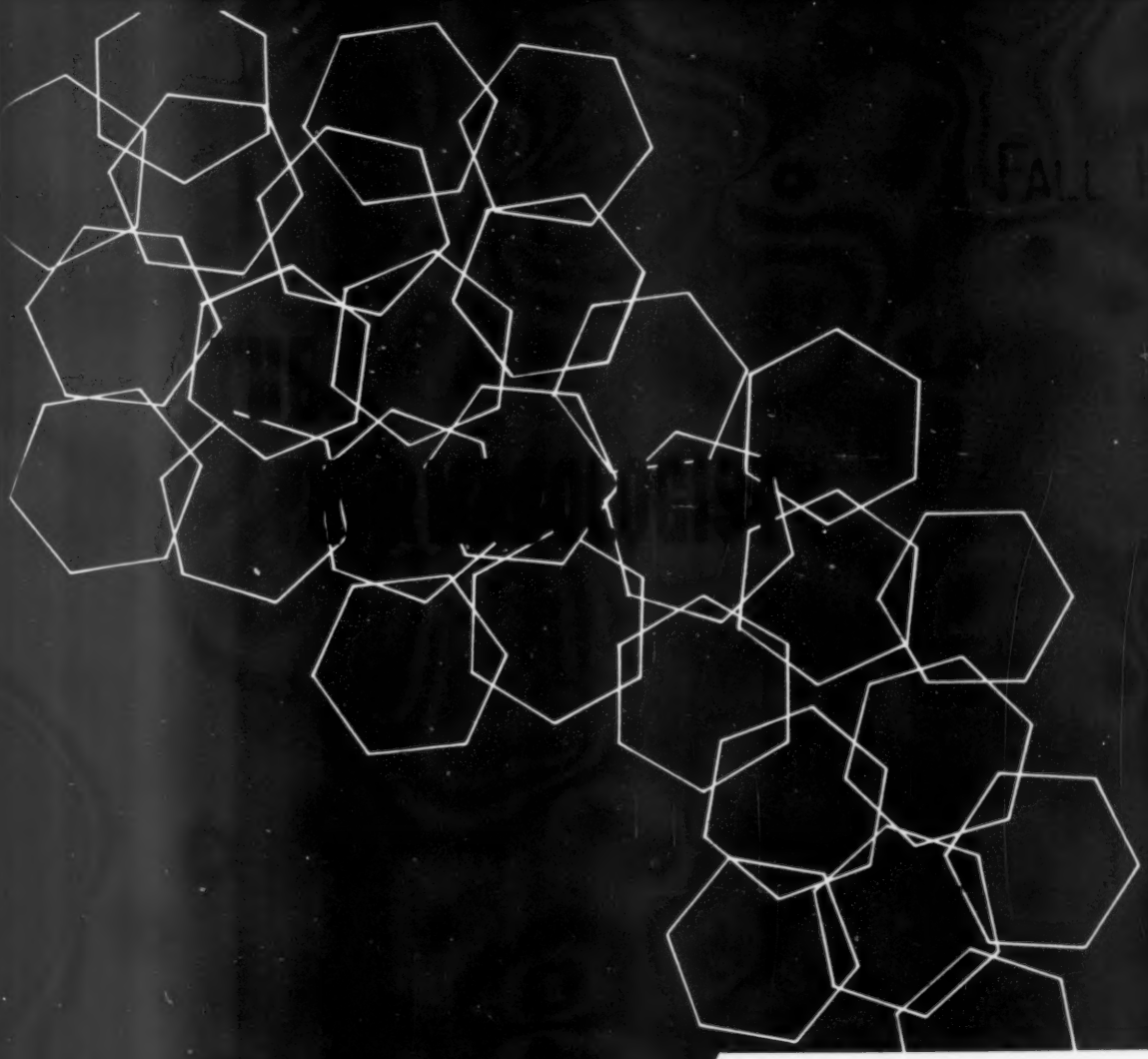

This Issue Contains Abstracts Of Papers To Be Presented At The Miami Meeting Of The Society, Aug. 31 - Sept. 3, 1959

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THE AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, INC.

President:	Louis S. Goodman (1960) University of Utah College of Medicine, Salt Lake City, Utah
President-elect:	Alfred Gilman (1960) Albert Einstein College of Medicine, New York 61, New York
Treasurer:	Allan D. Bass (1960) Vanderbilt University School of Medicine, Nashville, Tenn.
Treasurer-elect:	Frederick E. Shideman (1960) University of Wisconsin, Madison 6, Wisconsin
Secretary:	Karl H. Beyer (1961) Merck Sharp & Dohme Research Laboratories, West Point, Pa.
Past President:	Chauncey D. Leake (1960) The Ohio State University, Columbus 10, Ohio
Councilors:	Oliver H. Lowry (1960) Washington University School of Medicine, St. Louis 10, Mo.
	Robert M. Featherstone (1961) University of California School of Medicine, San Francisco 22, Calif.
	Walter F. Riker, Jr. (1962) Cornell University Medical College, New York 21, New York

Membership Committee
James A. Bain (1960), Chairman
George B. Koelle (1961)
W. Clarke Wescoe (1962)

Historian: E. M. K. Geiling

Committee on Financial Resources & Budget
A. D. Bass (1962)
K. H. Beyer (1962)
K. K. Chen (1960)
V. A. Drill (1961)
G. B. Koelle (1961)
Otto Krayer (1960)

Standing Committee on Educational Affairs
George Acheson (1961)
Allan D. Bass (1960)
Karl H. Beyer (1960)
Avram Goldstein (1962)
Louis Lasagna (1961)
Thomas H. Maren (1962)
Klaus Unna (1960)
To be appointed (1)

Nominating Committee
E. Leong Way, Chairman
T. Brody
A. Goldstein
S. Udenfriend
C. A. Winter

Committee on Professional Affairs and Public Relations
Ernest Bueding (1961)
Alfred Farah (1960)
Alfred Gilman (1960)
F. S. Philips (1961)
To be appointed (2)

Program Committee
Peter B. Dews (1961)
Neil C. Moran (1960)
Fred W. Schueler (1962)

Representatives to Council of AAAS
Gordon A. Alles
McKeen Cattell

THE AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, INC.

Representatives to the National Research Council

John C. Krantz, Jr. (Division of Medical Sciences) (1960)
Walter M. Booker (Division of Biology and Agriculture) (1960)

Representatives to International Union of Physiological Sciences

K. K. Chen
Otto Krayer
Carl F. Schmidt
James A. Shannon

Editorial Board, Journal of Pharmacology and Experimental Therapeutics

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Index Editor: R. M. Isenberger

Specific Field Editors:
H. L. Borison, Neuropharmacology
J. J. Burns, Drug Metabolism and Disposition
P. B. Dews, Psychopharmacology
Avram Goldstein, Biochemical and Cellular Pharmacology
Louis Lasagna, Clinical Pharmacology
N. C. Moran, Autonomic and Cardiovascular Pharmacology
G. H. Mudge, Renal Pharmacology and Electrolytes
J. A. Zapp, Jr., Toxicology

Julius Axelrod
H. K. Beecher
M. DeV. Cotten
E. F. Domino
W. W. Douglas
K. P. DuBois
Sydney Ellis
D. W. Fassett
R. F. Furchgott
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D. J. Jenden
Eva King Killam
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Norton Nelson
Barbara R. Rennick
W. K. Riker
Jay Roberts
F. W. Schueler
C. C. Smith
C. M. Smith
H. F. Smyth, Jr.
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E. W. Sutherland, Jr.
E. Leong Way
T. C. West
D. M. Woodbury
L. A. Woods

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Louis S. Goodman (1961)
Otto Krayer (1962)
George Koelle
Lawrence Peters

Secretary of Publications: Miss Eleanor Bates

REGARDING "THE PHARMACOLOGIST"

This represents the second number of "The Pharmacologist," in itself an experiment of The American Society for Pharmacology and Experimental Therapeutics. The need for a publication about pharmacology and The Society, especially for pharmacologists, has been discussed in Council meetings and from the floor of our business meetings. While there has not been an unanimity of opinion as to the need or function of such an organ, there has been a majority opinion that such an undertaking be launched. Our Past President and staunch advocate for "The Pharmacologist," Dr. Chauncey D. Leake, undertook the preparation of the first number, which appeared in the spring of 1959.

The present purpose of "The Pharmacologist" is to present in a semiannual publication such information of interest to the membership as might appropriately be handled in this manner. Such a general statement of purpose invites contributions and suggestions from the membership of the Society and its friends in allied sciences both in this country and from abroad. Indeed, one of the functions that such a communication might serve could be to bring to the Society information regarding our fellow pharmacologists from around the world, their officers, notices of their meetings, highlights of their organizations, etc. Certainly, "The Pharmacologist" may serve as a single medium for the circulation of information pertaining to Society affairs, such as the work of its several committees, abstracts of the fall meetings, notices, and the like.

It may take a few issues to establish the format and the usefulness of "The Pharmacologist." The Secretary of the Society earnestly invites your suggestions or criticism that may aid in assuring the success of this venture.

ANNOUNCEMENTS OF COMING MEETINGS

Federation of American Societies for Experimental Biology:
- 1960 - Chicago, Ill., Apr. 10-15
- 1961 - Atlantic City, N. J.
- 1962 - Atlantic City, N. J.
- 1963 - Atlantic City, N. J.

Fall Meetings of The American Society for Pharmacology and Experimental Therapeutics, Inc.:
- 1960 - Seattle, Washington, Aug. 21-25
- 1961 - Rochester, N. Y.
- 1962 - Nashville, Tenn.
- 1963 - San Francisco, Calif.

American Association for the Advancement of Science
- 1959 - Chicago, Ill. - Dec. 26-31

Western Pharmacology Society:
- 1960 - San Francisco, Calif., Jan. 21-23

Pharmacological Society of Canada:
- 1960 - Winnipeg, June 8-10

XXI International Congress for the Physiological Sciences:
- 1959 - Buenos Aires, Argentina, Aug. 9-15

German Pharmacological Society:
- 1959 - Basel, Switzerland, Sept. 29 - Oct. 2

RESUMÉ OF COUNCIL MINUTES

Atlantic City Meeting, April, 1959

For the first time, a budget prepared by the Committee on Financial Resources and Budget was presented at the business meeting. Included in the future will be the estimated costs of the Teaching Institute.

The military status of pharmacologists was reviewed on the basis of letters received by the secretary following an inquiry to the department chairmen throughout the country. A number of instances were found of pharmacologists who served in their specialty and also a number of instances in which inappropriate assignments were made for trained pharmacologists. Efforts continue to try to obtain recognition of pharmacology as a specialty.

Dr. Krayer has been appointed to the U. S. National Committee for the International Union of Physiological Sciences.

An ad hoc committee, headed by Dr. Henry K. Beecher, has been appointed to recommend a policy of editorial scrutiny on antivivisection questions.

Changing the name of the Society and changing the name of the Journal were discussed.

A proposition to set up a class of associate membership was discarded.

Dr. Uvnäs of Stockholm was present and joined in the discussion of possible international congresses.

The Board of Publication Trustees recommended that journal subscriptions not be tied to membership.

Read-by-title abstracts have been eliminated to keep us in accord with the action of the other societies.

A change in the bylaws has been authorized by the Council to include the means of designating our Federation Board members.

MINUTES OF COUNCIL MEETINGS
AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Hotel Ritz-Carlton, Room 316, Atlantic City, N. J.

Minutes of First Council Meeting
3:00 P.M., Saturday, April 11, 1959

Present: President Leake, Drs. Krayer, Featherstone, Beyer, Goodman, Brodie, Hodge.

The minutes of the Ann Arbor Council Meetings were approved.

Financial. Dr. Allan Bass presented the treasurer's report, including the audit submitted by Patty, Womack and Foster of Nashville, Tennessee. The report was discussed in detail and the treasurer was warmly thanked by the Council for his detailed portrayal of our present financial status. The treasurer was authorized to cash certain bonds that have now matured and to reinvest them in bonds. The treasurer stressed the importance of setting up a budget for the Teaching Institute a year ahead. For example, for the fall of 1959 the costs of the Teaching Institute are estimated as high as $1500, but no funds are appropriated or budgeted at the moment. President Leake sketched a sample budget on the blackboard, which initiated a discussion leading 1) to a suggestion that the name of the Committee on Financial Resources be lengthened to add "and Budget," and 2) to a request that this Committee prepare and bring in a budget later.

Military Status of Pharmacologists. The status of pharmacologists in the armed services was reviewed by Dr. Hodge on the basis of letters received by the secretary following a letter of inquiry to each pharmacology department chairman in the country. A number of examples of pharmacologists who served in reasonably well-suited jobs and a number of examples of pharmacologists who failed to find pharmacological assignments in the armed services were offered. President Leake referred to the Scientific Manpower Commission and reported that, since 1955, Meyerhoff says that pharmacologists have been classed as physiologists. The ease of confusion with pharmacists was stressed. President Leake was asked by the Council to find whether the extension of the draft law has appropriate consideration of pharmacologists written into it. Dr. Brodie pointed out that beginning in June the U. S. Public Health Service will list pharmacologists. They will start at the top of grade, like biochemists. Something still remains to be done, however, because travel expenses are not paid by the Public Health Service for incoming pharmacologists as they are for biochemists. It was the sense of the Council that we should ask P. K. Smith to continue his efforts to obtain a selective service assignment for pharmacologists and categories in the armed services.

Future Meetings. A schedule of future meetings was approved as follows:

1959	Fall	31 August - 3 September. Miami, Florida
1960	Spring	11-15 April. Chicago, Illinois
	Fall	21-25 August. Seattle, Washington

Minutes - Council Meetings

1961	Spring	Atlantic City, New Jersey
	Fall	Rochester, New York
1962	Spring	Atlantic City, New Jersey
	Fall	Nashville, Tennessee
1963	Spring	Atlantic City, New Jersey
	Fall	San Francisco, California

The invitation by Dr. Featherstone for the Pharmacology Society to meet in San Francisco in the fall of 1963 was accepted by the Council with thanks on a motion of Dr. Goodman, seconded by Dr. Beyer. The Council asked Dr. Krayer to inquire in Boston to ascertain, in the event that something prevented our meeting at Vanderbilt in the fall of 1962, whether Boston could be an alternate site. A brief discussion of the position of pharmacology in the international societies followed. The consensus emerged that our Society should be recognized under IUPS.

The arrangement of the program in the coming year was assigned by the Council following the precepts of Bylaw 4, Section 2, to the secretary of the Society together with the Program Committee. The current Atlantic City meeting includes 407 scientific papers, 3 read by title, 2 movies.

Resident Agent. Dr. G. H. Mudge was designated as the Resident Agent of the Corporation in Maryland, and a resolution thanking Dr. E. K. Marshall, Jr., our retiring and first Resident Agent, was read and approved for presentation to the Society.

The Committee on Professional Affairs' name was lengthened to include "and Public Relations." Interprofessional relations were entrusted to this committee and the responsibility for preparing public statements as needed from time to time was given to it.

Federation. Federation matters were considered. The Council recommended an intersociety session be proposed on Endocrines.

The Council did not favor lengthening the duration of the spring meeting, but preferred to lengthen each session, for example, to schedule papers from 8 to 12 A.M. and from 1 to 5:30 P.M., to meet Monday morning and, if necessary, Friday afternoon and Saturday.

Machine programming studies were approved as an excellent approach.

Our Council was prepared to go along with the recommendation of the Federation Board's Advisory Committee concerning costs of Federation Proceedings and, therefore, the amounts of Society assessments.

The Council asked that a letter of commendation be sent to the Federation secretary, Dr. Milton Lee, expressing satisfaction at the early mailing of the spring meeting programs this year.

Minutes - Council Meetings

9:50 A.M., Sunday, April 12, 1959

Present: President Leake, Drs. Krayer, Bass, Featherstone, Brodie, Goodman and Hodge.

Corporation Associates. The report on the activities of the corporation associates' program by Dr. Krayer revealed that inquiries directed to 33 companies had brought 30 answers and 30 contributions. Another contribution was in the mail making the total 31 contributions. The total sum collected is $10,300. The Council expressed satisfaction over this substantial support. There are two ways that this activity might move in the near future: a) a more personal approach to the officers of the companies might be made by some officer of the Pharmacology Society; b) income can be increased by bringing the $100 contributions to $250 or more. One means of increasing gifts would be to establish classifications or categories. It was generally agreed that Dr. Krayer could make a public announcement of the present status and success of the program by publishing a list of contributors and a description of the program in "The Pharmacologist." The secretary suggested that people in the Society give Dr. Krayer names of friends in various corporations. At Dr. Krayer's discretion, approaches might be made on his instructions and following the visit a report should be rendered to Dr. Krayer. There was some interest in wider solicitation of additional companies. Dr. Goodman asked that the Council request Dr. Krayer a) to continue with a strong hand, b) that he should broaden his base within his good judgement, for example, including chemical manufacturers, c) that he should write a statement of progress and purpose for "The Pharmacologist," listing present contributors and expanding with a concept of average contribution, and d) that a marked copy of "The Pharmacologist" be sent along with a tactful notice to the Corporation Associates next January. This motion was seconded by Dr. Featherstone and approved. President Leake amended to add a vote of warm and rich thanks to Dr. Krayer and authorized Dr. Krayer to have assistance in this program, specifically, the help of Dr. Goodman. This motion was approved.

Dr. Krayer asked whether members from industry should serve on the Committee on Financial Resources. It was generally agreed that, subject to the desires of the chairman (Dr. Krayer), this was proper. On the motion of Dr. Goodman, seconded by Dr. Hodge, the words "and Budget" were added to the name of the Committee, and the treasurer, president and secretary were made ex officio officers of this Committee. Motion approved.

Federation. Three changes in the Constitution and Bylaws of the Federation were discussed. These had to do with the description of the chairman of the Federation Board (article 4, Management), with the designation of members of the Board from each Society (article 3, Committees and Representatives) and with the title, Federation Secretary (article 2, the Federation Secretary). These three changes requested by the Federation Board were approved by the Council.

Dr. Van der Kloot raised an important question about the addition of information to symposia before publication but after the presentation of the symposium paper. Dr. Goodman suggested that the rules to authors be amended to ask that a footnote indicate any later data or any work done subsequent to the presentation of the paper. This was passed and recommended for consideration by the Federation Secretaries.

Past Presidents' Lunch. On the suggestion of President Leake that a past presidents' lunch be a regular feature of our spring meeting, Dr. Goodman moved, seconded by Dr. Hodge, that this lunch should bring together past presidents, Council and Board of Publication Trustees as guests of the Council. No official status is to be given past presidents, and no system is to be instituted for bringing matters to them or asking their official action. As a group of elder statesmen, however, their deep interest in and extensive experience with Society matters give the informal discussions of this group a remarkable value that the Society should capitalize on.

Representatives to the AAAS and the NRC were nominated at the request of President Leake.

The birth of "The Pharmacologist" led to a vote of thanks to President Leake, introduced by Dr. Goodman, seconded by Dr. Krayer. Dr. Leake described how "The Pharmacologist" was prepared for publication, typed by his own hands. The Council warmly applauded the energetic and imaginative work of President Leake for his successful attainment of this milestone in the history of the Society.

Dr. Brodie asked whether it would be possible to get funds from the Ford Foundation or some other foundation to support the Teaching Institute.

7:00 P.M., Sunday, April 12, 1959

Present: President Leake, Drs. Lowry, Featherstone, Beyer, Bass, Brodie, Goodman, Krayer and Hodge.

The treasurer's report was accepted and approved with thanks on a motion of Dr. Featherstone, seconded by Dr. Brodie.

President Leake appointed Dr. Krayer to the U. S. National Committee to replace Dr. Seevers. A resolution thanking Dr. Seevers for his effective work on behalf of the Society was approved on the motion of Dr. Goodman, seconded by Dr. Featherstone.

Dr. Beecher's letter asking for consideration of a policy to provide scrutiny of all papers from the point of view of antivivisection propaganda was discussed by Dr. Krayer. It seems entirely reasonable that the Council and the Board of Publication Trustees should have some stated policy on this matter. After discussion, it was voted on motion of Dr. Bass, seconded by

Dr. Lowry, that the Council should appoint an ad hoc committee to prepare appropriate recommendations. Motion carried. President Leake appointed Drs. Henry Beecher (chairman), Lawrence Peters and Harry Beckman.

The names of members who have achieved retired status during the past year were read and retired member status was confirmed for each of them.

Since Dr. E. M. K. Geiling, Historian of the Society, is one of those who is now a retired member, the Council approved a resolution asking Dr. Geiling to continue as the Historian of the Society at his pleasure.

The tax exempt status of the Society was reviewed by Treasurer Bass. Inquiry was directed through Dr. Mudge to the lawyer, McCarthy, who has recommended that the Society wait for protest before attempting to take any further steps (not that the Society is expecting a protest, but that no step need be taken until a difficulty appeared).

President Leake discussed the importance of having programs that would include the interests of the industrial toxicologists, and of the teachers of veterinary, dental and pharmacy courses in pharmacology. This idea was recommended to the Program Committee's attention.

Dr. Bass reported that the Educational Affairs Committee will discuss the standards of medical school courses in pharmacology.

The suggestion that pharmaceutical manufacturers should subsidize the alma mater of pharmacologists in their employ was not accepted.

A tentative budget put on the board by President Leake was referred to the Committee on Financial Resources and Budget.

The last item discussed was the question of changing the name of the Society. Ultimately, a straw vote showed eight favoring change and one against it. Two forms of a new name appeared to be attractive: 1) something like American Society for Pharmacology, 2) something like American Pharmacological Society.

Minutes of the Second Council Meeting
Jointly with the Membership Committee
9:00 A.M., Monday, April 13, 1959

Present: President Leake, Drs. Featherstone, Beyer, Goodman, Krayer, Hodge, Riker, Bain and Koelle.

There were 80 proposals brought by the Membership Committee. They recommended deferral on 11 and rejection of 2. Each application was considered. Each one marked for deferral or rejection was considered in detail. After an extended discussion, a list of 69 candidates was approved.

The Membership Committee recommended adversely on the suggestion that the Society adopt an associate member category.

Minutes - Council Meetings

The blank now titled "Application for Membership" is to be retitled "Proposal for Membership." A number of changes in the proposal form and in the check list were agreed on.

The Membership Committee recommended that members be elected only once a year. The Council approved.

There was a consensus that a geographical list of members is not needed.

On the nomination of honorary members, Dr. Krayer moved that the policy be set that this be a unanimous nomination by the combined Membership Committee and Council to be followed with the usual action by the Society.

Chairman Riker mentioned the fact that there were several late applicants this year which the Membership Committee decided to accept 1) because the list had been published and 2) because it was the first year of the new deadline. For these reasons, they were lenient. In the future, the deadline of July 1 will be rigidly enforced. Dr. Goodman asked the chairman of the Membership Committee to prepare or to certify the list of applicants in the future.

On a motion by Dr. Krayer, a statement to the Eli Lilly and Company was authorized to present our appreciation of their generosity in preparing the beautiful scroll for honorary members and particularly thanking the artists responsible for the design. The Scroll Committee, Dr. Krayer, chairman, Dr. Chen and Dr. Geiling were discharged with thanks.

Minutes of the Third Council Meeting
Jointly with the Board of Publication Trustees
1:00 P.M., Tuesday, April 14, 1959

Present: President Leake, Drs. Lowry, Brodie, Bass, Featherstone, Beyer, and Hodge. Board of Publication Trustees: Drs. Beckman, Goodman, Krayer, and Peters. By special invitation: Dr. Uvnäs.

The first topic discussed in order to obtain the advice and counsel of Dr. Uvnäs was that of International Congresses. Should Pharmacology negotiate for a separate International Congress or stay with the Physiologists? The excellent representation of Pharmacology in the top administration of IUPS was described. The fact that we have no funds for a separate Congress was stressed. We have an ad hoc committee on International Congresses, Chairman Brodie. Dr. Krayer suggested that ICSU should be contacted.

The current status of Beaumont House was discussed briefly. Our offices are now completely equipped. Miss Bates, our secretary of publications and her assistant, Mrs. June Whitson, are installed. Copy editing is now being done at Beaumont House after copy leaves the scientific editor. A good relation between the Beaumont House Office and Williams and Wilkins has been established and, as far as these matters are concerned, affairs are in good hands. The need for a central office is emphasized: at present Miss Bates and Mrs. Whitson spend

approximately one day each week on Society work. The Society pays at the moment $752.00 per year plus 15% overhead. A budget figure of $2500 for next year for expenses at Beaumont House has been set up.

At the request of Miss Bates, a letter of appreciation was voted to the Federation staff. Moved by Dr. Krayer, seconded by Dr. Goodman. Approved.

The Society mandate to seek an executive secretary-treasurer and to seek funds to support him is still binding on the Council.

A final report on the part of the editors was rendered for "Pharmacological Reviews" by Dr. Krayer as he retires. The Symposium on Catechol Amines is to be published as a supplement. Nine reviews have appeared this year. He now has copy for one or two issues ahead. There are 2,013 subscribers. The resignation of Dr. Krayer was accepted with regret and his great contributions acknowledged with applause. Dr. Krayer announced that Dr. Koelle will succeed him as editor. On a motion by President Leake, seconded by Drs. Goodman and Featherstone, our gratitude and appreciation to Dr. Krayer is written formally in the minutes. A resolution has been prepared by Dr. Goodman and was read before the Society at the annual dinner.

Dr. Peters reported on the status of the "Journal of Pharmacology and Experimental Therapeutics." He said that 268 manuscripts were received, which was about the same number as in 1956; 31% were rejected - some because they were clinical reports not suitable for the Journal. A total of 139 manuscripts were published in 1958; a new index in offset is in preparation. Several changes have been made, for example, the double format, the removal of the fall meeting abstracts, providing space for 15 to 17 additional manuscripts. Volumes were of unequal size during the past year. More space per manuscript can be gained by care in selecting the letter size of words in the figures. This will be specified in the future. As of 1959, there is about one month backlog. The new assistant editor carries about one-third of the load and has made a considerable difference in the many duties carried by the editor. There are eight specific field editors. An attempt will be made to get 348 pages per volume.

The secretary was put in charge of "The Pharmacologist." Material is to be sent to the secretary, thence to the secretary of publications, Miss Bates, for handling before publication.

A change in the name of the Journal is anticipated if the Society changes its name. The Council was of the unanimous opinion that the name should be changed to the "Journal of Pharmacology" in the event that the Society changes its name. Motion by Dr. Goodman, seconded by Dr. Bass. Carried.

The Board of Publication Trustees strongly recommended that Journal subscriptions not be tied to membership.

Our Council was not interested in restricting the distribution of journals by differentiating between member subscription rates and other rates as the Biochemists have done.

Minutes - Council Meetings

On a motion by Dr. Goodman, seconded by Dr. Featherstone, it was voted that in the future the desirability of subscribing to our journals be presented to new members by sending an order blank for the Journal and for the "Pharmacological Reviews" in the letter welcoming new members into the Society. The Council recommended to the Federation Secretaries the policy of capitalizing the initial letter of all trade names. (This action was later accepted by the Federation Secretaries and is to be made a part of the instructions to all authors.)

Dr. Jack Radomski, from the University of Miami, came in and gave a warm welcome to the Council in anticipation of the fall meeting at the University of Miami. He spoke of the availability of rooms, the desirability of air-conditioning for scientific sessions, the adequacy of facilities, the living rooms nearby and, lastly, setting the registration fee.

The non-archival nature of the abstracts of the fall meeting was again endorsed. Indexing by concept and by machine was mentioned. Several new journals have appeared in Pharmacology, including "Clinical Pharmacology and Therapeutics," Mosby, and "Psychopharmacologia," Springer. The Council expressed itself strongly opposed to naming official Society representatives to the editorial boards of non-society journals. The possibility that an "Annual Review of Pharmacology" may be started is still alive. Dr. Krayer called attention to one and all that he still has reprints of the "Symposium on Drug Antagonism" for sale at fifty cents each. He praised the value of this Symposium. He has several hundred reprints still available.

The report of the Committee on Educational Affairs was presented by Dr. Bass. A brief statement of their activities will be published in "The Pharmacologist."

The Committee on Financial Resources, through Dr. Krayer, presented a budget which was accepted and recommended for consideration at the Annual Business Meeting. A report by this Committee will be included in the summer issue of "The Pharmacologist." A report for the Committee on Professional Affairs and Public Relations was presented by Dr. Gilman; a summary report will be presented in "The Pharmacologist." A report of the activities of the Program Committee was summarized by Dr. Moran in the unavoidable absence of Chairman Furchgott. Dr. Moran described an innovation: workshops for a few graduate students to be held at the fall meeting. He also mentioned other plans and accomplishments of the Program Committee. The Council gave the Committee its warm applause and, in the words of Dr. Krayer, stated that we needed this Committee more than we knew. A report will appear in "The Pharmacologist."

The budget recommended by the Committee on Financial Resources and Budget is given in detail as follows:

Expense:	Federation	$ 3,200
	Beaumont House	2,500
	"The Pharmacologist"	1,000
	Secretary	2,500
	Treasurer	700
	Audit	150
	Meeting	800
	Contingencies	250
	Total	$11,100

It is easy to see that annual dues of $10 are not adequate; it was recommended that the dues be increased to $15.

On a motion of Dr. Brodie, seconded by Dr. Lowry, it was suggested that copies of a one-page advertisement of the new format of the Journal of Pharmacology and Experimental Therapeutics be widely distributed, e.g., to all our members. Dr. Goodman will talk with Williams and Wilkins who perhaps would run off some extra copies. The Board of Publication Trustees was asked to explore the cost with Williams and Wilkins.

The fall meeting will have a Teaching Institute, arranged by Dr. Welch, on the "Biochemical Aspects of the Mechanism of Action of Drugs." The question was raised as to whether next year perhaps we might have one on toxicology.

Dr. Bass stated that of the 145,000 brochures, 63,000 are left and requests are coming in such that about 1500 were sent out last month; 19,000 high schools have been circularized and copies have been sent to libraries and news services. Science teachers in colleges are the next to receive copies. In a reprint several additions will be made: 1) names of the Corporation Associates, 2) the departments offering graduate work, 3) list of fellowships available, and 4) a card for the student to fill in with places for him to check for special interests in curriculum or kind of school, etc. It was suggested that a line be included stating that Dr. Justin Powers could be asked for information about graduate work in pharmacology in colleges of pharmacy. The Council passed a resolution of pleasure and amazement in the continued imaginative progress and the extraordinary accomplishments of the Committee on Educational Affairs. This was passed unanimously. The Committee next year estimated that something like $15,000 will be needed for its work. An NIH grant for this amount has been applied for. Dr. Allan Bass signed for the Society.

The income from Corporation Associates will go to the Committee on Educational Affairs if the grant is not received. The amount on hand at present (about $10,000) is not as much as the Committee on Educational Affairs asked for, so that their present budget would have to be amended.

On the motion of Dr. Krayer, seconded by Dr. Hodge, Society dues were set at $15 for 1959-60. Approved by Council.

Dr. Gilman discussed the problem of the pharmacologist in relation to world medical research (the statement that Senator Humphrey asked for).

The question of the American Medical Association's Committee on Paramedical Groups was opened. President Leake spoke tellingly of his effective appearance before the Committee. Dr. Goodman was instructed to carry the sentiments of the Council about the attitudes of the AMA to the AMA Committee he serves on.

Minutes of the Fourth Council Meeting
2:00 P.M., Thursday, April 16, 1959

Present: President Leake, President-elect Gilman, Drs. Bass, Shideman, Beyer, Riker, Featherstone, Goodman and Hodge.

The complicated arrangement for handling and distributing the registration fee for the spring meeting next year (involving moneys for individual societies) makes it impossible for the Council to bill our members as had been decided, specifically indicating the assessment for Federation membership. On the motion of Dr. Krayer, seconded by Dr. Featherstone, it was moved that bills be sent to the members simply asking for $15 dues.

It was moved by Dr. Featherstone, seconded by Dr. Riker, that Dr. Goodman's resolutions presented at the annual dinner become part of the minutes of the Society. Carried.

Dr. Goodman mentioned the importance of Council support and of Society action on a resolution endorsing the principle that professional societies might receive grants for recruitment. The Council recommended to the Society on the motion of Dr. Goodman, seconded by Dr. Hodge, that the resolution be adopted requesting support of recruitment (but specifying that the government employees present had abstained from voting). Moved by Dr. Krayer, seconded by Dr. Beyer. Carried. Drs. Goodman and Hodge were asked to write this resolution.

In line with the action of the Federation Secretaries on the motion of Dr. Hodge, seconded by Dr. Beyer, the Council approved eliminating "read by title" abstracts.

The Council instructed the secretary to ask Dr. Munson if he would head the first intersociety session on Endocrines as authorized by the Federation Secretaries.

The secretary was instructed to send to the Program Committee a suggestion from President Leake that an intersociety session on antibiotics be organized. The Federation will mail material describing our Societies' needs in the fall mailing if received prior to November 15. It was agreed that this was a good thing to do.

The official means of designating Federation Board Members is to be written into the bylaws, on a motion by Dr. Featherstone, seconded by Dr. Riker, and approved by the Council. This item must be formally presented in the spring letter.

Dr. Gilman resigned as chairman of the Committee on Professional Affairs and Public Relations. His resignation was received with regret.

The report of the ad hoc Committee on Food Additives was presented by Chairman Hodge. The Committee was thanked and discharged. A list of 100 names of experts from which can be selected panel members to adjudge the safety of common additive materials to foods has been sent to Commissioner Harvey of the Food and Drug Administration.

Minutes - Business Meetings

For the business meeting of the Society, it was suggested that next year the trial ballots should be colored and the final ballots white. Color differences could also be used for the proposed members lists.

MINUTES OF THE BUSINESS MEETING
AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Ritz Hall of the Hotel Ritz-Carlton, Atlantic City, N. J.

4:30 P.M., April 14 and 16, 1959

President Chauncey Leake Presiding

The minutes of the Ann Arbor meetings were approved as published.

The report of the Nominating Committee was accepted on a motion by Dr. Krayer. Nominations from the floor were limited to the names of the present Nominating Committee.

The following officers were elected for 1959-1960:

President	Louis S. Goodman
President-elect	Alfred Gilman
Treasurer	Allan D. Bass
Treasurer-elect	Frederick E. Shideman
Secretary	Karl H. Beyer, Jr.
Past President	Chauncey D. Leake
Councilor	Walter F. Riker, Jr.

The report of the Membership Committee was presented by Chairman Riker. Names of candidates recommended by the Council and by the Membership Committee were posted.

Dr. Leake reported on the state of the Society. He deplored the small number of members who subscribe to Society journals - only a third of our membership subscribe. He listed some of the benefits the Society members gain through their membership: for example, the publications of the Federation, such as the directory, the program, the abstracts, the symposia, a total of 1400-plus pages a year. The registration fee for the spring meeting in 1960 will be increased to cover the rising costs of publication and of the other functions of the Federation. The letters from the President and now the new informal journal, "The Pharmacologist," are some of the benefits for members. Dr. Leake spoke at some length concerning the American Medical Association's interest in the so-called paramedical fields. He stressed the importance of promoting wholesome, mutually respectful interrelations.

Treasurer Bass reported on the status of Society funds, stressing the fact that we actually spent some $3,000 over our income this year. The Treasurer's report had been audited. Dr. Goodman moved acceptance, which promptly carried.

Minutes - Business Meetings

Dr. Krayer described the activities of the Committee on Financial Resources and Budget, and presented a Society budget for the next fiscal year. On the recommendation of the Council the dues have been set at $15 for the next year. Dr. Ferguson suggested economy by eliminating "The Pharmacologist." However, a straw vote indicated, by approximately 2 to 1, disfavor of this suggestion. Dr. Bass stressed the fact that a good many expenses on behalf of the Society, for example, in the secretary's office, are not charged to the Society and that presently we must take care of all our operating costs. A unanimous vote accepted the first budget including the $15 dues for next year.

Dr. Krayer reported for the Board of Publication Trustees. The secretary of publications, Miss Eleanor Bates, and her assistant, Mrs. June Whitson, are established in Beaumont House and the office is functioning smoothly (copy editing after the copy leaves the scientific editor). Dr. Krayer retires this year as Editor of "Pharmacological Reviews" and will be succeeded by Dr. George B. Koelle. Dr. Peters reported a busy year for the "Journal of Pharmacology and Experimental Therapeutics": the new format, non-archival abstracts for the fall meeting, an assistant editor, Dr. Moran, and eight "specific field editors."

A new Resident Agent for the Corporation in Maryland, Dr. Gilbert H. Mudge, has been appointed. A resolution thanking Dr. E. K. Marshall, Jr. offered by the Council was presented by Dr. Lowry and unanimously approved.

An amendment of the constitution adding titles to certain articles was carried on a motion by Dr. Koelle, unanimously. An amendment of the bylaws was carried for the first vote (providing for election of Honorary Members exactly like regular members). Announcements were made about changes in the constitution of the Federation.

The program of future meetings is as follows:

Spring Meetings -	1960, Chicago, Illinois
	1961, Atlantic City, New Jersey
	1962, Atlantic City, New Jersey
	1963, Atlantic City, New Jersey
Fall Meetings -	1959, Miami, Florida
	1960, Seattle, Washington
	1961, Rochester, New York
	1962, Nashville, Tennessee
	1963, San Francisco, California

The past-presidents' luncheon, an innovation, on Thursday noon was announced.

The discussion of whether the Society should change its name was a lively one. A new possible name would be the American Society for Pharmacologists. Dr. Richards was in favor of keeping "Experimental Therapeutics" in the title to prevent confusion with the activities of pharmacists. Dr. Van Maanen thought we could save some money by not having to type the three extra words in the title, but that originally these words were needed in order to tie pharmacology in with clinical activity. Dr. Garb thought that the words, "Experimental Therapeutics," convey a medical connotation and would keep people from confusing

pharmacology with pharmacy. Dr. Rieders mentioned the broad scope that the name indicates. Dr. Brody thought that this was a question of education. One member thought we should appeal to the clinicians and furthermore the tradition and sentimental attachment were important. Perhaps we should also include such names as experimental osteopathy if we talk about experimental therapeutics. Dr. Knoefel spoke on the possible new names.

Dr. Krayer reported the activities of the editorial office of "Pharmacological Reviews" and officially offered his resignation. The Society extended its gratitude and warm thanks to Dr. Krayer in accepting his resignation. Dr. Goodman's resolution read at the dinner has become a part of the minutes. Dr. Peters presented the report of the editors of the "Journal of Pharmacology and Experimental Therapeutics." This will become a part of the record in "The Pharmacologist."

Thursday Afternoon Business Meeting

The bylaws change was moved and carried for the second and final vote.

A number of announcements were made about Federation affairs, for example, of the 2,484 abstracts, only 24 needed to be recopied. A new intersociety session on endocrines was announced.

Election of members was conducted. New members (elected in 1958) were asked to rise and give their names. About 10 were present. The scrolls for the new Honorary Members, Drs. Richards, Sollmann and Voegtlin, were on exhibit at the rear of the hall.

Necrology notices were read for the following deceased members:

William B. Draper	February 18, 1958
Jack King Finnegan	September 13, 1958
Marion S. Dooley	December 13, 1958
Eugene F. DuBois	February 12, 1959

A list of members who retired during the past year was read as follows:

E. M. K. Geiling	George H. Miller
James C. Rice	W. F. von Oetteingen
Arthur L. Bloomfield	

The change in the name of the Society and also possibly a change in the name of the Journal were the subjects of active discussion. The discussion will be reopened at the fall meeting. Possibly sooner or later a mail ballot will be offered so that everyone will have an opportunity to express an opinion.

Dr. Allan Bass, Chairman of the Committee on Educational Affairs, reported that the fall meeting will present a Teaching Institute on the "Biochemical Aspects of the Mechanism of Action of Drugs" lead by Dr. Arnold Welch. About 80,000 brochures on "Careers in Pharmacology" have been mailed out. A grant application for support of this work by funds from the Public Health Service has been filed.

Minutes - Business Meetings

The Program Committee report was presented by Dr. Furchgott. The fall meeting will include a few introductory papers by chairmen of scientific sessions giving orientation and a broad view of the field with special reference to the problems to be presented in the 10-minute papers. Workshops in which a few leaders in certain fields will spend a few hours with a small group of graduate students or recent post-doctoral graduates will be offered.

The development of the Corporation Associates' plan was described by Dr. Krayer. The Society now has received a total of $10,800 through this plan. On a vote to decide whether the Society should increase its effort and widen the scope of this plan, there was an over-all majority in favor, with enough nay votes to indicate a current of opposition.

Dr. Goodman offered a resolution in support of the proposition that professional societies be permitted to receive Federal funds to aid in recruitment.

Dr. Otto Krayer was recommended by the President after consultation with the Council as the new member of the Board of Publication Trustees. This nomination was accepted by the Society.

The ad hoc Committee on Food Additives (Chairman Hodge, DuBois, Maynard) reported that a list of names of possible experts, who might serve to judge the safety of certain food additives, has been sent to Commissioner Harvey at his request. The Committee was discharged.

In a secret vote, 69 new regular members were elected, making a total of Society membership of 869.

There were 263 members who signed in on the membership lists at the first meeting and 165 at the second meeting.

CONGRATULATIONS AND A HEARTY WELCOME
TO THE NEWLY ELECTED MEMBERS OF THE
AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

Honorary Membership

Alfred N. Richards
Torald Sollmann
Carl Voegtlin

Regular Membership

Elijah Adams
John D. Arnold
Walter E. Barrett
William R. Beavers
Carmen T. Bello
Donald R. Bennett
Rudolf P. Bircher
Paul Brazeau
David A. Brodie
Theodore G. Brown, Jr.
Joseph P. Buckely
Peter H. Bulle
Alfred Burger
Marcus N. Carroll, Jr.
Mary Kathleen Carter
William Clark
Jack R. Cooper
Lawrence E. Detrick
Otho D. Easterday
James R. Fouts
Morris E. Friedkin
James R. Gillette
Charles N. Gillis
Harold F. Hardman
Clare T. Harwood
Francis Herr
Sidney Hess
Gerhard J. Hildebrand
Duncan Holaday
Francis W. Hughes
Oleg Jardetzky
Herbert J. Kayden
Alexander D. Kenny
Samuel Kuna
Digby Leigh
Frank J. Macri
Gertrude Maengwyn-Davies
Bernard H. Marks
William Martin
William L. Miller, Jr.
William Morse
Edmund F. Murtha
John W. Nelson
Norton Nelson
Margaret K. O'Gara
Claudia S. Prickett
Gertrude P. Quinn
William K. Riker
Joseph M. Ritchie
George Rowe
LeRoy H. Saxe, Jr.
Richard W. Schayer
Roger W. Sevy
Jean Sice
Henry F. Smyth, Jr.
Virginia L. Sydow
Ralph E. Tedeschi
Eberhard G. Trams
Robert C. Troop
Edward J. Walaszek
Sidney S. Walkenstein
Donald P. Wallach
Vaman S. Waravdekar
James R. Weeks
Irwin M. Weiner
Norman Weiner
Bob West
Richard P. White
John A. Zapp, Jr.

Reports

Report of the Board of Publication Trustees

1. The new publishing contract with Williams & Wilkins.

After one year of operating under the new contract, it is not yet possible to say how much more favorable the financial situation of the Society will be. Creeping inflation counteracts many of our moves. But we are in the black under present operating conditions, with a well functioning Editorial Office at Beaumont House.

2. Activities at the Beaumont House office.

The office is now completely equipped for the copy-editing work of the Society. Miss Eleanor Bates, Secretary of Publications, has worked out the copy-editing routines for the Journal and for the Reviews. Assisted by her Editorial Assistant, Mrs. June Whitson, she is responsible for all material to be published from the time it has left the hands of the scientific editors until it appears in print. The editorial office has established good working relations with Waverly Press and with our publishers, Williams & Wilkins.

Recently, the efficiency and work capacity of the office was put to a severe test by the need for publishing a supplement to Pharmacological Reviews. This is a supplement of approximately 320 printed pages containing the contributions to the Symposium on Catecholamines. It was paid for by the National Institutes of Health under a grant to the Pharmacology Study Section and will be distributed free of charge to the subscribers to Pharmacological Reviews. Miss Bates and Mrs. Whitson have taken care of this extra load of work efficiently and fast. It can be said that our journals are in very competent hands so far as copy-editing is concerned.

The need for a central office of the Society at Federation headquarters for other than editorial tasks is underlined by the experience of the past few months. Already about one 8-hour work day per week is absorbed by work of our copy-editor and her assistant for the Society. Inquiries of various kinds come to the office and certain Society mailings apart from publishing matters are dispatched from there.

3. The Executive Secretary-Treasurer and Managing Editor.

This part of an earlier mandate of the Society remains unrealized. We are still searching for the right man; and we are seeking the necessary funds to support him. There will probably be more to say on this matter a year from now.

Otto Krayer

Reports

Report of the Chairman of the Editorial Board on "Pharmacological Reviews" for 1958-59

During the year 1958, nine reviews were published totaling 512 pages, making up Volume 10 of Pharmacological Reviews.

The first issue of Volume 11, containing three reviews, has appeared. The second issue will contain three reviews. Together with this the subscribers will receive the Symposium on Catecholamines.

Seven reviews are in various stages of editorial appraisal and revision. Nine more are promised for 1959. We are nearing the hoped-for state when we can prepare printer's copy for one or two numbers ahead. This is of great importance for a steady work schedule of our editorial office at Beaumont House.

According to the latest report from Williams & Wilkins the subscription list of Pharmacological Reviews now stands at 2013.

The Editorial Advisory Board suddenly lost one of its members, E. Braun-Menéndez from Argentina, who died in an airplane accident.

There has been no change to date in the composition of the Editorial Board. However, the Board of Publication Trustees has accepted my resignation as Chairman of the Editorial Board, and I am happy to announce to the Society that Dr. George B. Koelle has agreed to be my successor. This report then, is my last report to you as Chairman of the Editorial Board of Pharmacological Reviews. The task was often difficult and at times exasperating. However, it was always deeply rewarding because there was the support of your confidence and there was the unqualified cooperation and unstinting service and devotion to duty of the Editorial Board members, past and present. I shall treasure to the end of my days the memory of this joint labor of love.

Now that the task is done and Dr. George Koelle is taking over, I wish to pay a debt of gratitude -- in which I am sure you will join -- to Dr. Louis Goodman, who set such a splendid example of performance as our first editor of Pharmacological Reviews.

Otto Krayer

Reports

Report of the Editor of the "Journal of Pharmacology and Experimental Therapeutics"

The following is a report of editorial activities relating to the Journal of Pharmacology and Experimental Therapeutics, primarily for the year 1958.

The first table presented below concerns the disposition of manuscripts received during the calendar year 1958, the information being complete to April 1, 1959. The table also presents comparable data for the three preceding years.

	1958	1957	1956	1955
Accepted for publication	139	142	182	171
Combined with others	3	1	1	2
Withdrawn by authors	4	6	4	11
Sent for revision, not yet returned	38 (14%)	29 (12%)	16 (6%)	3
Rejected	84 (31%)*	73 (29%)	68 (25%)	64 (25.5%)
Total manuscripts received	268	251	271	251

* In this category were 15 manuscripts (5.6%) which were classed as "non-scientific" since they contained no actual data or lacked all semblance of experimental design; hence their rejection was automatic.

The number of manuscripts submitted in 1958 represents a slight increase over the number submitted in 1957 and 1955, but is approximately the same as in 1956. Again, as in 1957, a heavy load of manuscripts was received late in the year, hence more manuscripts are still out for revision than there were at a comparable time in earlier years. Of the manuscripts rejected, 7 have been resubmitted as new manuscripts with additional experimental data. At this writing, 3 of these have been accepted. It should be added that minor changes in the manner of classifying and handling manuscripts were introduced in mid-1957 with the new Editor and Editorial Board. Hence, the figures presented above for different years are not strictly comparable.

The actual publication statistics for the calendar year 1958 are presented below in comparison to previous years.

	1958	1957	1956
Manuscripts from 1955	0	1	81
Manuscripts from 1956	0	101	85
Manuscripts from 1957	77	75	--
Manuscripts from 1958	68	--	--
Total manuscripts published	145	177	166

Reports

		1958	1957	1956
Pages published:	Vol. 122	531* (371)**		
	Vol. 123	453 (315)		
	Vol. 124	512 (356)		
		1496 (1042)	1634	1504
Contractural page allotment		1500 (1044)	1500	1500
Pages devoted to abstracts		85	67	66
Pages per manuscript		9.6 (6.6)	8.9	8.7

* Page figures outside of parentheses are in terms of single column format.
** Pages inside parentheses are in terms of double column format.

A few remarks supplementary to these publication statistics seem pertinent. 1) A new space-saving double-column format was introduced with Vol. 123 to compensate for a marked increase in printing costs. The new format permits publication in a 348-page volume of the same amount of material as that published previously in a 500-page volume based on a single-column format. Pages for 1958 are therefore given in terms of both types of format and page allotment. 2) The annual contractural page allotment of 1500 single-column (or 1044 double-column) pages of text for the year was adhered to because all accumulated page credit was consumed in 1957 in order to eliminate a backlog of manuscripts. 3) The page figures given do not include the index. The new index is longer than that published prior to 1958 but is done in offset at a cost which is only 35% of that of regular printed pages. 4) Abstracts will not be published in the Journal in the future, hence the space previously devoted to these will be available for full manuscripts. 5) There was a significant increase in the pages used per manuscript in 1958. 6) The uneven distribution of pages between the three volumes of 1958 was necessitated by "cutoffs" coincident with changes in format and style.

The Assistant Editor is currently functioning as the Specific Field Editor for the largest single area. The Editor-in-Chief coordinates the entire operation and continues to serve as the regular Editor for manuscripts which do not fall into the area of responsibility of any of the eight Specific Field Editors. One or two additional Field Editors may be appointed. This new system recognizes the fact that a single Editor cannot be optimally competent in all areas and also serves to make the load of editorship more feasible as an addition to other full-time duties. It is hoped that the recognition of the various fields as areas meriting highly qualified editors, who are actively engaged in them research-wise, will encourage the submission of more manuscripts within these and, in fact, within all areas of pharmacological investigation. Since the system has been invoked so recently, no statement concerning its effectiveness can yet be made.

Reports

The members of the Editorial Board deserve continued commendation for their services. They have given their time very freely and generously to this volunteer work for the Society, and I would like to thank them officially for their devotion to their editorial duties. We have on 25 occasions sought the additional assistance of consultant reviewers within the Society. They have likewise been most helpful, despite the unexpectedness of our requests.

In closing, I would like to thank the Board of Publication Trustees and the members of the Society for the help and cooperation which they have extended to the Editorial Board and to me during the past year.

Respectfully submitted,

/s/

Lawrence Peters, Editor

Report of the Chairman of the Committee on Educational Affairs

Packages of 400 or more brochures have been sent to departments requesting them, some departments having requested as many as 1500. These have been sent out for local distribution in the areas in which the respective schools are located. Brochures have been distributed to career advisers and science teachers in 19,000 high schools; they have been sent to 600 libraries and to approximately 700 teachers of biology and chemistry in small colleges throughout the United States. Between three and four thousand inquiries have been received at our Washington office since the brochures have been distributed. The supply of brochures is running low and will need to be reprinted for next year's distribution. The Committee wishes to include in the next distribution a list of all schools offering graduate programs in Pharmacology. Those departments interested in being listed should forward their names to the Chairman of the Committee in the near future.

Means of establishing minimum standards for graduate education in Pharmacology were discussed by the Committee, and although it is realized that this is an important problem, no action was taken at this time. The Committee plans a survey of the status of graduate education in Pharmacology again this coming year. It is necessary if we are to assess the impact of our recruitment efforts.

Allan D. Bass

Report of the Chairman of the Committee on Financial Resources and Budget

The Chairman informed the members of the Committee of the change in duty of the Committee on Financial Resources to include responsibility for setting up an annual budget for the Society. The name of the Committee was therefore changed to Committee on Financial Resources and Budget by action of the Council.

The Chairman reported on the result of the drive for Corporation Associates. The financial return to date amounts to $10,300 in contributions varying from $100 to $1,000, with an average of about $400. It was decided to continue the drive to attract more pharmaceutical firms and perhaps chemical manufacturers to become Corporation Associates of the Society. The recommendation for the use of funds is as follows. Legitimate uses of the funds from income from Corporation Associates dues are:

1) Salary and expenses of the Executive Secretary-Treasurer, at such time as he shall be appointed.

2) Educational affairs of the Society with special regard to the recruiting of pharmacologists at present undertaken by the Committee on Educational Affairs.

The following uses are considered not to be legitimate:

1) Subsidy of regular publications of the Society except in the initiation stage of the publication of a new journal of the Society. Use of funds from dues of Corporation Associates is to be limited to the time when the printing and publication costs of the new journal are not covered fully by the income from subscribers.

2) Salary of the Managing Editor.

3) Salaries of the Secretary of Publications and of the Editorial Assistant.

The plan to secure an Executive Secretary-Treasurer who could at the same time take over the function of Managing Editor was discussed further. The consensus of opinion was that it is better to find a younger executive officer rather than seek to attract one of the retired professors of pharmacology to serve for an interim period of a few years.

The question of a tie-in of subscriptions to the Journal of Pharmacology or to Pharmacological Reviews with the membership fee was discussed and unanimously rejected.

Reports

The budget of the Society for the year 1959-60 was considered, and the following table of income and expenses was drawn up on the basis of an estimated membership of 840.

Dues	$10 per member		$ 8,400.
Expenses:	Federation assessments	$ 3,360.	
	Beaumont House Office - Society activities	2,500.*	
	The Pharmacologist	1,000.	
	The office of the Secretary of the Society	2,500.	
	The office of the Treasurer	700.	
	Audit of Treasurer's report	150.	
	Meetings	800.	
	Contingency Fund	250.	
	Total	$ 11,260.	

* The sum of $2,500 for Society expenses at Beaumont House was arrived at as follows: the time the Secretary of Publications and the Editorial Assistant spend on Society matters amounts to approximately 1/10th of their combined time. In addition, the rent of the Beaumont House office per year amounts to $750. Taking into account an overhead of 15% brings the total expense to the approximate level of $2500.

On the basis of this budget it is obvious that the dues of $10 per member do not cover our expenses. The minimum required would be $13.40 per member. The Finance Committee voted unanimously to recommend to the Council and to the Society an increase in the membership fee for 1959-60 from $10 to $15. (A unanimous vote of acceptance of this report was accompanied by the adoption of an increase in membership dues to $15. See Minutes of Society Business Meetings, April 14 and 16, 1959.)

Otto Krayer

The American Society for Pharmacology and Experimental Therapeutics
acknowledges with grateful appreciation
its
CORPORATION ASSOCIATES

Abbott Laboratories, Incorporated
Bristol Laboratories Inc.
Burroughs Wellcome & Co. (U.S.A.) Inc.
CIBA Pharmaceutical Products Inc.
Cutter Laboratories
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JOHNSON & JOHNSON
Lakeside Laboratories, Incorporated
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The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana
McNeil Laboratories, Inc.
The Merck Company Foundation
Wm. S. Merrell Company
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S. B. Penick & Company
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Smith Kline & French Laboratories
Sterling Winthrop Research Institute of Rensselaer, New York
Squibb Institute for Medical Research
The Upjohn Company
Wallace Laboratories, Division of Carter Products, Inc.
Warner-Lambert Research Institute
Wyeth Institute for Medical Research

Resolution of Appreciation
to
Dr. E. K. Marshall, Jr.
Emeritus Professor of Pharmacology
The Johns Hopkins University School of Medicine
and
First Editor of The Journal after
it became the property of The Society

The members of the American Society for Pharmacology and Experimental Therapeutics express to Dr. E. K. Marshall, Jr. their deep appreciation of his outstanding contributions to the advancement of our Society through his efficient management of the Journal of Pharmacology and Experimental Therapeutics after The Journal became the property of our Society.

It was on April 9, 1933, at a special meeting of the American Society for Pharmacology, held in Cincinnati, Ohio, that Professor John J. Abel, the founder and owner of the Journal of Pharmacology and Experimental Therapeutics, offered to transfer to the Society all his rights and privileges in the said Journal. The President of the Society, the late William deB. MacNider accepted Dr. Abel's gracious offer on behalf of the Society amid prolonged applause. Dr. Abel briefly reviewed the history of the founding of the Journal and its subsequent development.

Dr. E. K. Marshall, Jr. was the unanimous choice of the Society as Editor-in-Chief of the Journal. He was empowered to make the necessary arrangements for the transfer of the Journal to the Society; to negotiate a new contract for the printing and publishing of the Journal by the Williams and Wilkins Company of Baltimore, Md.; to select an editorial board of five or six members; to draft editorial board policies; and to engage legal counsel to execute a new certificate of Incorporation for the Society, with the corporation headquarters in Baltimore, Maryland. He also acted as the local agent of the newly incorporated Society. All these duties required a great deal of time and patience. Through Dr. Marshall's untiring efforts the Journal has achieved a high standard of excellence and is in a financially sound position. He relinquished the Editorship of the Journal after ten years in 1944, and has now requested that he be relieved of the responsibility of acting as the local agent of the Journal.

The Society was extremely fortunate in having Dr. Marshall as its first editor. He established an excellent pattern for future editors of the Journal. The Society extends its sincere thanks and its best wishes for many years of good health to enjoy the leisure which he so richly deserves.

This motion is to become a part of the permanent record of the American Society for Pharmacology and Experimental Therapeutics, Inc.

Prepared by E. M. K. Geiling.
Adopted by the Society at its Business Meeting, April 14, 1959.

Resolution of Appreciation
to
Dr. Otto Krayer
Professor of Pharmacology
Harvard University School of Medicine

On his retirement as
Editor of Pharmacological Reviews

At its business meeting on April 14, President Leake extended to Professor Otto Krayer the thanks and the respect of our Society for his five years of devoted service as Editor of Pharmacological Reviews. It was announced that a more formal resolution to this effect would be entered into our records, and these brief comments are designed for that purpose.

Despite his many duties, his responsibilities to his University, and his many other services to this Society, Professor Krayer accepted the Editorship of Pharmacological Reviews five years ago, when asked to do so by the Board of Publication Trustees. Under his Editorship, the Reviews has maintained a high standard of excellence and grown considerably in stature and in number of subscribers. He has kept the Reviews the truly international publication that it was intended to be, has attracted a most distinguished group of scientists to its editorial board, and has found a most competent person to be his successor. Few of us realize the growing pains - intellectual and financial - suffered by the Reviews in its early years. It was an infant when Professor Krayer undertook to nourish it, to cure its ills, and to put flesh on its skeleton. It is now a husky and healthy adolescent, and one can see the shape of the man to come. Professor Krayer has been both the mother and the father of the Reviews, and his parthenogenetic skill is admired by all who have followed the affairs of this journal. Last summer, at our 1958 fall meeting in Ann Arbor, the Society paid a warm tribute to Professor Krayer for many other services well rendered. On this occasion, it extends to him our thanks and gratitude for five years of editorial labor which has made Pharmacological Reviews one of the most respected biological journals in the world.

Prepared by Louis S. Goodman.
Adopted by the Society at its Business Meeting, April 16, 1959.

Resolution of Appreciation
to
Dr. Harold C. Hodge
Professor of Pharmacology
University of Rochester Medical Center

On his retirement as
Secretary of the Society

Without the usual excessive number of "Whereases" and "Be it Resolved," the American Society for Pharmacology and Experimental Therapeutics owes and hereby pays to Dr. Harold Hodge a deep debt of gratitude and respect for his three long years of hard labor as the Secretary of our Society. This position is the most difficult one which our Society imposes on its favored few. It entails long hours of service and much sacrifice of time, energy, patience and peace of mind - more profitably spent in one's laboratory, in one's home, and in the capture and enjoyment of the niceties of life. In all the multifaceted aspects of his work as our Secretary, Dr. Hodge has exhibited the efficiency, the good humor, and the kindliness which has won for him a central position in the pharmacological sun and endeared him to all members of our Society. He has kept our Presidents straight, our Treasurers solvent, our Committees functioning, and our members informed. Only those intimately associated with Society affairs really know the labor of love which Dr. Hodge has performed for us and for our discipline. How he has managed to do all this and still retain his sanity and equanimity is one of Nature's well-guarded secrets. Dr. Hodge has surely earned his release from work and worry as our Secretary. But we warn him not to relax by means of persisting depolarization. For such men are hard to find and, after a decent interval for his recuperation, our Society may again call upon him for another period of matchless service in a less traumatic and more rewarding capacity. We extend to Dr. Hodge our gratitude and our thanks for a task superbly performed, and our best wishes for his future.

Prepared by Louis S. Goodman and Otto Krayer.
Adopted by the Society at its Business Meeting, April 16, 1959.

AVE ATQUE VALE

Chauncey D. Leake, Past President

The Japanese poets, in their effort toward an economy of beauty, have developed a formal verse of 17 syllables, arranged 5-7-5 in three lines. This is a "haiku," and is an exercise for appropriate sentiment on appropriate occasion. Traditionally, a "haiku" should include some reference to nature, and to a season of the year. Here then is a "haiku" fitting for my first greeting to you all as your past president:

Like green growth in Spring,
Advance of our group shows health,
Brings joy to us all!

The American Society for Pharmacology and Experimental Therapeutics, Inc. is really growing. Around 10 per cent new membership each year is substantial evidence of good health in the rapidly expanding discipline of pharmacology with all that the science implies.

Many changes have occurred in the Society since the Washington meeting at the end of December in 1924 when I was admitted to membership, under the sponsorship of my revered teacher at the University of Wisconsin, Professor A. S. Loevenhart (1878-1929). He had proposed me when I was admitted to the American Physiological Society, but the pharmacologists thought I was too young and really not well enough established. In those days our Society was really an honor group.

There was much talk about the growing dangers to the discipline of pharmacology through the rapid increase in the pharmaceutical industry in our country. Any member of the Society who might go into industrial pharmacology was dropped from membership. However, the many important contributions from industrial pharmaceutical laboratories during the 30's gave ample evidence of high scientific standards, and presently the membership rulings were changed, and our Society became proud of its industrial leaders and of their practical achievements.

Something of the same sort of situation continues to confront us. Our Society is still in the process of converting itself from an honor organization to a service group. Traditionally, pharmacology and toxicology have been associated with the profession of medicine. Most of the practical applications of scientific development in pharmacology and toxicology have been applied to therapy. Even here, however, the picture is widening, to include the applications of pharmacology in the diagnosis of disease and the prevention of disease, as well as to the cure of disease or to the alleviation of symptoms of disease. Pharmacology is also becoming widely applied in agriculture and in all the other health professions, including dentistry, pharmacy, nursing, veterinary medicine, sanitary engineering and public health. Pharmacology is even becoming applied in sociology, criminology, warfare and law.

Ave atque Vale - Leake

How far should our Society go in extending membership to scientists who are contributing to pharmacological and toxicological knowledge and advance, no matter what their academic, industrial or governmental positions may be, nor no matter what applications may be made of their scientific contributions?

This matter of membership in our Society becomes pertinent in connection with the increasing number of distinguished contributing pharmacologists who hold academic positions in colleges of pharmacy, in veterinary schools and in schools of dentistry, as well as in industrial and governmental agencies. How far can our Society aid in maintaining over-all worthy standards of scientific undertaking in these various categories? How far can our Society go in trying to establish worthy standards for teaching in pharmacology, whether in professional schools or in graduate schools? What role can our Society play in bringing together the various health professions in more satisfactory interprofessional relations, contributing to the welfare and benefit of society as a whole?

There are many important social problems confronting the peoples of the world as a result of the current scientific explosion. We are getting so much knowledge about ourselves and our environment that we don't know quite what to do with it all. And we are creating for ourselves enormous problems such as: (1) overpopulation, (2) radiation hazards, (3) pollution of airs and waters, (4) racketeering involving legal aspects of drug control, with particular reference to drug addiction, and (5) socially moral responsibilities of scientists. Many of these problems concern pharmacology. Are these problems appropriate for consideration by the American Society for Pharmacology and Experimental Therapeutics, Inc.? Will people, the world over, expect pharmacologists to give leadership in connection with appropriate solutions to some of these problems?

Many of these problems are already being considered by the American Association for the Advancement of Science, of which your past president is now President-elect. These problems are troubling peoples all over the world. We have been enormously successful in our scientific advance of many fronts, particularly including the control of disease. This has vastly increased life expectancy, and thus brought with it the problems of overpopulation and what to do with our increasing number of old people, who are not prepared to take care of themselves and for whose care no one else is prepared either. The ever present threat of war bothers peoples everywhere, and what are we going to do about it? Is it appropriate for the American Society for Pharmacology and Experimental Therapeutics, Inc. to consider its social responsibilities in making available scientific information on the action of chemical agents on living material, so that worldwide satisfying public policies may be developed from this information?

No longer is it possible for scientists to retire to some quiet sheltered haven or go off in some secluded tower to escape the realities of social responsibilities. We have a job to do right in the busy market places of the world and in the places where public policy decisions are being made.

Ave atque Vale - Leake

If we can meet the challenge of our social responsibilities in a way that indicates our concern for the welfare of peoples everywhere, we are much more likely to obtain respectful hearing and favorable consideration than if we are to turn ourselves toward seeking social support for our own personal or group endeavors. We can best serve ourselves by serving people everywhere. This widening of our horizons of responsibility is certain to be beneficial to us, in the inner satisfactions it can bring us all in doing for people what they expect us to do for them and for which they support us.

The rapid expansion of the scientific discipline of pharmacology is well reflected in the many new periodicals devoted to publishing and distributing contributions in the field. These new pharmacology periodicals fill a need. Our Society could, in my opinion, well afford to be generous in giving support and backing to these new journals. From evidence already offered, the publishers of these new pharmacology journals would be willing to make reductions in subscription rates to members of the American Society for Pharmacology and Experimental Therapeutics, Inc., in return for aid in sponsorship and in solving policy problems. This might include aid in editorial affairs. Many of the members of our Society cooperate in these ways already.

These new journals, however, are not enough. We are accumulating so many factual details about the actions of chemicals on living material that we are in danger of suffering from intellectual indigestion in regard to them. Somewhere we must work out a method whereby we may have an annual index of pharmacological publications, and then more reviews and surveys of selected fields of current interest in pharmacology and toxicology. Our own Pharmacological Reviews is the leader in the review field in the discipline. Its reviews are excellent, timely, critical and very skillfully edited. Reviews of this sort are the most effective way of covering a field with which one may not be familiar in detail, and they are the best way to introduce new research workers into special areas of investigation in pharmacology.

It now appears that an Annual Review of Pharmacology will appear. This is fine. This will not be as critical as the carefully organized reviews which appear in Pharmacological Reviews, but it will provide an opportunity for an annual survey of significant contributions in the various and widely expanded fields of research interest covered by pharmacology and toxicology.

Years ago your past president was very skeptical about the development of Annual Review of Physiology. He felt that it would compete with Physiological Reviews. He felt that also it would not be wise for the American Physiological Society to cooperate in the editing and development of Annual Review of Physiology. He was very wrong! The Annual Review of Physiology fills an extremely important need, in giving an opportunity to physiologists to survey annually significant advances in the broad field of physiological research. It has never interfered with the character or growth of Physiological Reviews. There is every reason to expect that the Annual Review of Pharmacology, under the wise editorial direction of Windsor Cutting, will fill a great need for pharmacologists all over the world and increase the understanding and appreciation of pharmacological development by scientists.

There is still much to be thought about. What should we do about promoting an International Congress in Pharmacology and Toxicology? There are broad areas of research in pharmacology in other countries with which we are not particularly familiar. We do not ordinarily take the time regularly to go over pharmacological reports from abroad, nor do we scan foreign scientific periodicals very satisfactorily. The result is that we may be missing matters that may be quite worthwhile. Nor does the International Congress of Physiological Sciences quite satisfactorily cover the field of pharmacology and toxicology. The biological chemists have set up an international congress. Maybe we had better strive toward something of this sort in regard to pharmacology. Whatever can promote better international contacts among scientists will contribute to better world understanding and to the betterment of welfare among peoples everywhere. We might well afford to take the leadership in this matter.

Thus, in saying "Hail and Farewell" at the end of my term of office as President of the American Society for Pharmacology and Experimental Therapeutics, Inc., I am saluting pharmacologists and toxicologists everywhere. I am wishing them well in their scientific endeavors. I am hoping that they will derive rich and lasting satisfactions from their scientific work. I am hoping that they will accept the challenges of leadership offered to them in this exciting time. I am grateful for the chance I have had to participate actively in organizational affairs relating to pharmacology and toxicology, and I pray that I might still have an idea or two worthwhile for consideration as we continue to go along. Ave atque Vale is an ancient term of respectful salutation. I am using it with the deepest regard for my colleagues in a thrilling scientific endeavor.

DECENNIAL MEETING OF THE U.S.P. CONVENTION

Individual members of the American Society for Pharmacology and Experimental Therapeutics have long taken an active interest in the U. S. Pharmacopeia both at the decennial meetings and during the intervening period of active revision. This has had the effect of almost making the Society a patron of the Pharmacopeia from the standpoint of medical representation.

The next decennial meeting of the Pharmacopeial Convention is scheduled for March 29-30, 1960 in Washington. All accredited medical schools are entitled to send delegates. In many of these schools, the head of the Pharmacology Department undoubtedly will be consulted in selecting the delegate.

The decennial meetings of the convention are generally concluded in two days during which time an organization is set up, through election, for the succeeding decade. The organization consists of officers, a Board of Trustees to direct the general policy of the Pharmacopeia and to manage its business affairs, and finally, a Committee of Revision to produce two revisions of the Pharmacopeia during the succeeding decade. The Committee also issues supplements in addition to revising the entire book at five-year intervals.

A special effort is being made now, in preparation for the 1960 Convention, to acquaint physicians with the Pharmacopeia and its purposes. By this means it is hoped that the pressing problems of conducting the revision program may receive thorough consideration with a view to providing directives for the ensuing ten years. It is highly important, therefore, that in selecting this delegate a person be named who is either already quite familiar with the Pharmacopeia as an institution or who will undertake to familiarize himself with it and with the problems that it faces.

DR. K. K. CHEN: PRINCIPAL SPEAKER AT THE PHARMACOLOGY DINNER

We are indeed privileged to have as the after-dinner speaker at the Pharmacology dinner on Tuesday evening during the Miami meeting Dr. K. K. Chen, Director of Pharmacological Research, Eli Lilly Research Laboratories. Dr. Chen is one of the foremost members of the Society by virtue of his contributions to research and of service to this organization. As an investigator, his first claim to fame came with his classic research on ephedrine. For many years he has maintained an interest in cardiotropic principals derived from the toad. Indeed, the subject of his talk will deal with the folklore, the history and the scientific aspects of toad poisons. This combination of an excellent and a fascinating subject should be a highlight of the meeting.

SCHEDULE OF SESSIONS
August 31 - September 3, 1959

	Memorial Building				
	Beaumont Lecture Hall	Room N-202	Room N-204	Room N-205	
MONDAY - 9:00 A.M. - 1:30 P.M.	Teaching Institute	---	---	---	
MONDAY - 7:00 P.M.					Workshop Sessions
MONDAY - 8:30 P.M.					Smoker
TUESDAY - 9:00 A.M.	Psychopharm-acology I	Cardio-vascular I	Cell. & Bio-chem. Pharm. I	Kidney and Electrolytes	
TUESDAY - 1:30 P.M.	Neuropharm-acology I	Cardio-vascular II	Cell. & Bio-chem. Pharm. II	Autonomic Pharmacol. I	
TUESDAY - 7:00 P.M.					Pharmacology Dinner
WEDNESDAY - 9:00 A.M.	Neuropharm-acology II	Cardio-vascular III	Drug Metabolism	Autonomic Pharmacol. II	
WEDNESDAY - 1:30 P.M.	Psychopharm-acology II	Cardio-vascular IV	Toxicology	Nerve and Muscle	
WEDNESDAY - 4:15 P.M.	Society Busi-ness Meeting				
THURSDAY - 8:30 A.M.	Society Busi-ness Meeting				
THURSDAY - 9:00 A.M.	Monoamine Oxidase Inhibitors	Cardio-vascular V	Analgesics	Chemotherapy & Endocrinology	

TEACHING INSTITUTE

Monday, August 31, 1959

"BIOCHEMICAL ASPECTS OF THE MECHANISM OF ACTION OF DRUGS"

Chairman: Dr. A. D. Welch

Department of Pharmacology,
Yale University, New Haven, Conn.

Morning Session:

1) Biochemical Studies on the Binding of Amines in the Tissues

Dr. G. V. R. Born

Nuffield Institute for Medical Research,
Oxford, England

Certain kinds of cells have the ability to store pharmacologically active amines. The amines are concentrated in intracellular granules, and recent work suggests that the granules contain specific constituents to which the amines are bound. The following summarizes what is known of the binding of amines in adrenal medullary cells, in mast cells and in blood platelets.

The catecholamines are present in high concentration in the cells of the adrenal medulla. From these cells granules have been isolated which contain most of the amines (Blaschko, Hagen and Welch, 1955). The granules have been separated from mitochondria from which they differ morphologically (Fig. 1; Burgos and Fawcett, unpublished; Wetzstein, 1957) and biochemically (Fig. 2, 3 and 4; Blaschko, Hagen and Hagen, 1957). There are at least two kinds of granule, one of which contains mainly epinephrine and the other mainly norepinephrine (Schümann, 1957).

The catecholamines account for up to 19% of the dry weight of the granules (Hillarp, 1958), which also contain adenosine phosphates, mainly the triphosphate (ATP), in extraordinarily high concentrations, i.e. up to 13% of the dry weight: there are about 3.9 moles of catecholamine for each mole of the adenosine phosphates (Table 1). Since at pH 7.2 the catecholamines carry one positive charge and ATP about 3.8 negative charges, the results suggest that the catecholamines are associated with ATP by ionic forces (Blaschko, Born, D'Iorio and Eade, 1956; Hillarp, 1958). Similar granules are present in sympathetic nerves (Schümann, 1958).

When adrenal granules are suspended in hypotonic solutions, the catecholamines and ATP are released in similar proportion (Fig. 5, Blaschko et al., 1956). When insulin is injected into rabbits or sheep the adrenal medullae are stimulated via the sympathetic nerves; the fall in the concentration of the catecholamines is accompanied by a proportional fall in ATP concentration. When stimulation ceases, the concentrations of amine and ATP slowly increase together (Carlsson, Hillarp and Hökfelt, 1957; Fig. 6, Hornykiewicz, unpublished results).

How stimulation releases the substances is not known; the blood stream may receive whole granules (Carlsson et al., 1957), or only their contents (De Robertis and Vaz Ferreira, 1957).

Histamine is present in many tissues. Mast cells contain histamine in high concentration, so that tissues rich in mast cells, e.g. dog liver and ox pleura, are also rich in histamine (Fig. 7 and 8, Riley, 1959). However, some other tissues which have few or no mast cells also contain histamine, e.g. the pyloric mucosa of rats (Riley, 1959). Histamine which is injected into animals is not retained in the tissues, even if most of their histamine is first removed (Schayer and Smiley, 1954). Injected histidine, however, gives rise to bound histamine. Mast cells can form not only histamine (Schayer, 1956) but, in mice and rats, also serotonin (Table 2, Furth, Hagen and Hirsch, 1957; Lagunoff, Lam, Roeper and Benditt, 1957; Hagen and Lee, 1958). The amines are not broken down in mast cells: although they contain amine oxidase, the enzyme does not catalyze the oxidation of histamine or serotonin (Hagen, 1959). There is evidence to suggest that in mast cells histamine and serotonin are bound ionically to heparin; all three substances are found in intracellular granules which are morphologically and biochemically distinct from mitochondria (Fig. 9, Hagen, 1959; Barnett, Hagen and Lee, 1958). From the results of Cass, Riley, West, Head and Stroud (1954) one can calculate that in tumours of mast cells in dogs the number of negative charges provided by the sulphonic acid groups of heparin is similar to the number of histamine molecules present.

In vitro, histamine can form a complex with heparin (Sanyal and West, 1956) and with phospholipids (Lindahl, 1955). Histamine reacts with phospholipids, as shown by a change in their physical state at an interface between two liquids (Hirt and Berchtold, 1952).

Serotonin is found in high concentration in the enterochromaffin cells of the intestinal wall and in blood platelets. The enterochromaffin cells (Fig. 10) contain 5-hydroxytryptophan decarboxylase which catalyzes the formation of serotonin.

Platelets do not produce serotonin; they are able to take up serotonin present in the fluid in which they are suspended. This uptake has been demonstrated with circulating and with isolated platelets (Fig. 11, Erspamer, 1956; Weissbach, Bogdanski and Udenfriend, 1958; Hardisty and Stacey, 1955; Zucker and Borrelli, 1956). Serotonin in platelets can exchange with serotonin present

in plasma, but such an exchange cannot be demonstrated in living animals because their plasma contains very little serotonin (Fig. 12, Born and Gillson, 1959; Udenfriend and Weissbach, 1954). Recent work indicates that serotonin diffuses into platelets and is then taken up by granules which are present in the cytoplasm (Fig. 13, Born and Bricknell, 1959; Fig. 14, Low and Freeman, 1958; Blaschko and Born, to be published). In the granules serotonin probably becomes associated with ATP, but it seems that the process by which serotonin reaches the ATP cannot be accounted for by simple diffusion (Born and Gillson, 1959).

Discussion: Amine accumulation and binding. Cells which accumulate amines either produce them (adrenal medullary and mast cells) or take them up actively (platelets). The rate at which amines cross the cell membrane is slow (Born and Bricknell, 1959; Born, unpublished results; Blaschko, 1954). It is, therefore, possible that cells accumulate amines while the rate at which they are formed or taken up exceeds the rate at which they diffuse out of the cell.

This, however, is unlikely to account for the high content of amines in storage cells, the granules of which bind amines after the cell itself has been disrupted. The presence in the granules of acidic substances in concentrations equivalent to those of the basic amines suggests that they are associated by ionic forces. If the adenosine phosphates and heparin are attached to particulate constituents of the granules their amine-binding system is analogous to a cation exchange resin. Such a system could account for some observations on the release of the naturally occurring amines by other basic substances (Paton, 1957).

The affinity of the binding material is greater for some amines than for others (Sanyal and West, 1956). These differences presumably depend upon the fit of the amine to the binding site around the acidic group, so that forces other than ionic ones determine the specificity of amine binding.

Amine receptors. According to Ehrlich's hypothesis, substances which produce effects in living tissues do so by combining with specific chemical groupings, called "receptors," on or in the cells. The acidic substances with which the naturally occurring amines are associated in storage granules may be thought of as receptors for the amines. Their existence suggests that secreting and smooth muscle cells which are affected by the amines may have receptors which are similar to those in storage granules. The rapidity with which the amines produce their effects and the ease with which they are abolished by reducing the amine concentration indicate that the interaction between amine and receptor is tenuous. This kind of interaction may well be brought about by ionic forces similar to those which dominate the binding of amines in storage granules. Presumably there are additional forces between amine and receptor which account for the specificity of their interaction.

Physiological significance of amine binding in stores. Although the storage cells contain high concentrations of the amines they are pharmacologically inactive. In platelets, for example, however high the concentration of serotonin

it does not affect the rate of movement of potassium into the platelets (Table 3, Born, 1958). The intracellular binding of amines makes it possible, therefore, to inactivate them without destroying them. Only after their release from storage cells into the body fluids do the amines produce their characteristic effects. Recently it has been found that in nerve endings acetylcholine is also contained in granules which are released when the nerve is stimulated (del Castillo and Katz, 1956; Whittaker, 1958). It seems, therefore, that reserves of many active substances are maintained in inactive form by being stored in intracellular granules.

References:

Barnett, R. J., Hagen, P., and Lee, F. L. (1958). Biochem. J., 69, 36P.
Blaschko, H. (1954). Pharmacol. Rev., 6, 23.
Blaschko, H., Born, G. V. R., D'Iorio, A., and Eade, N. R. (1956). J. Physiol., 133, 548.
Blaschko, H., Hagen, J. M., and Hagen, P. (1957). J. Physiol., 139, 316.
Blaschko, H., Hagen, P., and Welch, A. D. (1955). J. Physiol., 129, 27.
Born, G. V. R. (1958). In Abstracts of the Communications to the Fourth International Congress of Biochemistry. London: Pergamon.
Born, G. V. R., and Bricknell, J. (1959). J. Physiol. (in the press).
Born, G. V. R., and Gillson, R. E. (1959). J. Physiol., 146, 472.
Carlsson, A., Hillarp, N. A., and Hökfelt, B. (1957). J. Biol. Chem., 227, 243.
Cass, R., Riley, J. F., West, G. B., Head, K. W., and Stroud, S. W. (1954). Nature, Lond., 174, 318.
De Robertis, E., and Vaz Ferreira, A. (1957). Exp. Cell Res., 12, 568.
del Castillo, J., and Katz, B. (1956). Progr. Biophys., 6, 121.
Erspamer, V. (1956). J. Physiol., 133, 1.
Furth, J., Hagen, P., and Hirsch, E. I. (1957). Proc. Soc. Exper. Biol. & Med., 95, 824.
Hagen, P. (1959). Fed. Proc., 18, 399.
Hagen, P., and Lee, F. L. (1958). J. Physiol., 143, 7P.
Hardisty, R. M., and Stacey, R. S. (1955). J. Physiol., 130, 711.
Hillarp, N. A. (1958). Acta physiol. Scand., 42, 321.
Hirt, R., and Berchtold, R. (1952). Arzneimittel-Forsch., 2, 453.
Lagunoff, D., Lam, K. B., Roeper, E., and Benditt, E. P. (1957). Fed. Proc., 16, 363.
Lindahl, K. M. (1955). Acta physiol. Scand., 35, 146.
Low, F. N., and Freeman, J. A. (1958). Electronmicroscopic Atlas of Normal and Leukemic Human Blood. New York: McGraw-Hill.
Paton, W. D. M. (1957). Pharmacol. Rev., 9, 269.
Riley, J. F. (1959). The Mast Cells. Edinburgh: Livingstone.
Sanyal, R. K., and West, G. B. (1956). Nature, Lond., 178, 1293.
Schayer, R. W. (1956). Amer. J. Physiol., 186, 199.
Schayer, R. W., and Smiley, R. L. (1954). Amer. J. Physiol., 177, 401.
Schümann, H. J. (1957). J. Physiol., 137, 318.
Schümann, H. J. (1958). Arch. exp. Path., 233, 296.
Udenfriend, S., and Weissbach, H. (1954). Fed. Proc., 13, 412.
Weissbach, H., Bogdanski, F., and Udenfriend, S. (1958). Arch. Biochem., 73, 492.
Wetzstein, R. (1957). Z. Zellforsch., 46, 517.
Whittaker, V. P. (1958). Biochem. J., 68, 21P.
Zucker, M. B., and Borrelli, J. (1956). Amer. J. Physiol., 186, 105.

2) Mechanism of Glycogenolytic Action of Epinephrine

Dr. T. W. Rall and Dr. E. W. Sutherland

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The rate of glycogenolysis in liver, and in various types of muscle, is related to the tissue level of active phosphorylase. The catecholamines increase the tissue levels of active phosphorylase in liver, diaphragm, skeletal muscle, heart, rabbit uterus, and perhaps increase the levels in certain other tissues. As a result the levels of hexose phosphates in tissue are increased, and, depending on the organ studied, an increased output of glucose or lactic acid may be observed. The relation of these changes to various effects of epinephrine on muscle tissue, especially cardiac tissue, is currently under study in several laboratories. The interconversion of phosphorylases to active and inactive forms involves removal of phosphate from a serine residue by a phosphatase and its replacement by transfer of phosphate from ATP in a kinase reaction. The phosphorylase kinase in crude broken cell preparations or extracts appears to be under restraint. In homogenates of liver, this restraint tended to be removed by epinephrine, so that epinephrine greatly stimulated the formation of active phosphorylase from the inactive form in these cell-free preparations. It was found that the particulate portion of homogenates was essential for the hormone effect and formed a heat-stable factor, later identified as 3',5' cyclic AMP which stimulated the kinase reaction (phosphorylase activation) in extracts where epinephrine had no effect. The formation of 3',5' cyclic AMP from ATP in particulate preparations of liver, heart or skeletal muscle was stimulated by epinephrine. The relative potency of sympathomimetic amines in preparations from dog liver was very similar to that observed in causing hyperglycemia in the intact animal, l-norepinephrine being about 16 per cent as potent as l-epinephrine. However, in preparations of dog heart ventricle, l-norepinephrine was about two times and l-isopropylarterenol nearly twenty times as potent as l-epinephrine in stimulating 3',5' cyclic AMP formation. This is similar to the relative potencies of these agents in bringing about inotropic and chronotropic effects in preparations of the dog heart. Thus, it appears that the receptors for glycogenolysis are very similar to or perhaps are identical with those for inotropic and chronotropic effects. Tissues which are capable of forming 3',5' cyclic AMP are also capable of destroying it. Heart muscle has been a rich source of an enzyme which converts 3',5' cyclic AMP to 5' AMP. Caffeine and theophylline inhibit this enzyme which fact explains why these agents increase the accumulation of 3',5' AMP in particulate preparations forming the cyclic compound and may be related to the cardiac inotropic effect of methyl xanthines. It may be concluded that catecholamines promote the activation of phosphorylases of certain tissues and that the resulting glycogenolysis may help explain some of the effects of these amines. It seems clear, however, that the effect on phosphorylase is a result of a more immediate action on the formation of 3',5' cyclic AMP. Other possible effects of this cyclic nucleotide have not been fully explored; one report of changes in ketone body formation suggests another effect of 3',5'cyclic AMP. The form-

ation of 3',5' cyclic AMP is influenced by several hormones and its preservation is influenced by the methyl xanthines. A number of earlier references may be found in the review article by Ellis (Pharmacol. Rev., 1956); others will be included in an article for Pharmacological Reviews in preparation.

3) Bacterial Cell Wall Synthesis:
Its Relation to the Mechanism of Action of Antibiotics

Dr. J. L. Strominger

Department of Pharmacology,
Washington University, St. Louis, Mo.

A number of antibiotics owe their selective toxicity for microorganisms to inhibition of bacterial cell wall synthesis. Various stains show the cell wall as a well defined structure external to the cytoplasmic membrane. It lies between the membrane and the capsule in encapsulated bacteria. Cell walls are prepared by fragmentation of bacteria with glass beads followed by separation of walls by differential centrifugation (Salton and Horne). Such preparations appear in electron micrographs as empty envelopes - globular in the case of cocci and sausage-shaped in the case of bacilli. Cell walls of some intact bacteria are digested by egg-white lysozyme. The resulting globular protoplast, with its limiting cytoplasmic membrane, explodes in media of ordinary tonicity but can be stabilized in hypertonic media (Weibull). These experiments define the bacterial cell wall as the rigid outer membrane which gives form and shape to a microorganism and serves to protect it from such deleterious influences as osmotic shock. The cell walls of gram positive organisms have a relatively simple composition, containing only 3 or 4 amino acids, a few sugars and, in some cases, a phosphopolyalcohol. These constituents are arranged in a "basal structure" (accounting for perhaps 90% of the wall) and a relatively small "special structure." No lipid is present. On the other hand the more complex walls of gram negative organisms contain protein, polysaccharide and from 8-30% lipid. These walls also contain a "basal structure" similar to that in the wall of gram positive organisms, but representing only about 20% of the wall. The remainder is "special structure."

Two independent lines of investigation led to the hypothesis that penicillin is an inhibitor of cell wall synthesis. In hypertonic media, penicillin, like lysozyme, induces the formation of protoplasts of E. coli, suggesting that penicillin was selectively influencing the integrity or synthesis of the cell wall (Lederberg). In S. aureus, uridine nucleotides accumulate under the influence of penicillin. The principal nucleotide contains an acetylamino sugar-peptide fragment. A striking similarity between the compositions of this fragment and the composition of the "basal structure" of the cell wall suggested that the uridine nucleotide is a cell wall precursor and that nucleotide accumulation is the consequence of inhibition of cell wall synthesis (Park and Strominger). This scheme is analogous to the role of uridine nucleotides in synthetic reactions in general (e.g. glucuronide synthesis) which will be briefly reviewed. Isotopic data support the hypothesis that penicillin in-

hibits cell wall synthesis in E. coli and in S. aureus in a similar manner (Nathenson and Strominger). The relative insensitivity of E. coli to penicillin is probably the consequence of inability of the antibiotic at low concentration to penetrate through the lipid barrier in the outer wall.

Other penicillins (including cephalosporins), bacitracin and novobiocin inhibit cell wall synthesis in a manner similar to penicillin when viewed in terms of the nucleotides which accumulate. Blocks at other points in cell wall synthesis are induced by (1) oxamycin (D-cycloserine), (2) lysine deprivation and (3) gentian violet. The site of these lesions will be discussed in relation to current knowledge of enzymatic mechanisms in cell wall synthesis. Among these substances inhibition by oxamycin is most completely understood. It is a competitive inhibitor of incorporation of D-alanine into the uridine nucleotide (and hence into the cell wall). The molecular basis for this competition is evident from its structure. Its enzymatic basis has been partly defined and will be discussed. This study provides the first example of definition of the mechanism of action of an antibiotic at an enzymatic level. The selective toxicity of some antibiotics is, therefore, the consequence of interference in metabolic reactions which lead to the synthesis of unique microbial structures, not found in animal cells.

Afternoon Session:

4) Agents Which Influence Nucleic Acid Metabolism

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The synthesis of nucleic acids has been a primary target in the search for chemotherapeutic agents which might alter the course of parasitic and neoplastic diseases. A number of 4-amino derivatives of pteroylglutamic acid have achieved an important role in the treatment of acute leukemia in children and chorioepithelioma of women while other anti-folic derivatives, such as the diamino-dihydro-pyrimidine, pyrimethamine, are useful in certain types of plasmodial infections. The blockade by these compounds of the enzymic systems responsible for the reduction of pteroylglutamic acid to the various tetrahydrocoenzyme forms of this vitamin results in sharp curtailment of the synthesis of the adenine and guanine, and particularly, of the thymine components of nucleic acids. Similarly, blockade of the synthesis de novo of purines has been achieved with the glutamine antagonists, O-diazoacetyl-L-serine and 6-diazo-5-oxo-L-norleucine (DON).

A more direct approach has been the design of compounds which are close structural analogs of the natural purine and pyrimidine bases. 6-Mercaptopurine, 2-thioguanine and 8-azaguanine are examples of compounds with marked carcinostatic activity which probably function as anti-metabolites after conversion in the cell to the corresponding ribonucleotides. Although certain of

these purine antagonists are incorporated into the nucleic acids of affected cells, it does not appear that the formation of such fraudulent nucleic acids is the primary mechanism of action of these compounds. Generally, they are considered to produce a blockade in the formation or subsequent utilization of adenine and guanine nucleotides. Such a blockade interrupts protein and nucleic acid synthesis and perhaps other cellular reactions catalyzed by co-enzymes containing these bases.

Replacements of H on the 5-position of the pyrimidine ring by halogens or other groupings has produced a large number of compounds which are antagonists of the synthesis or utilization of thymine derivatives essential for the assembly of deoxyribonucleic acid. Among the most promising of these are 5-fluoro-uracil and its deoxyribonucleoside. Although 5-fluoro-uracil inhibits several enzymatic reactions, its primary site of action appears to be the conversion of deoxyuridylic acid to thymidylic acid. This reaction, which involves the transfer by a tetrahydro-folic acid-dependent enzyme of a one-carbon unit, is profoundly inhibited by 5-fluoro-deoxyuridylic acid, a metabolite of this analog. The corresponding chloro-, bromo-, and iodo- uracils are readily incorporated into deoxyribonucleic acid in lieu of thymine, and the deoxyribonucleosides of iodo- and bromo-uracil exert carcinostatic effects on a number of experimental neoplasms; however, their precise mechanism of action has not yet been defined.

The uracil analog, 6-azauracil (an asym-triazine derivative), inhibits the growth of a number of microorganisms and experimental tumors. The ribonucleoside of the compound, azauridine, is a more effective inhibitor and has been shown to exert its action primarily after conversion to the phosphorylated derivative, azauridine-5'-phosphate. Although it is formed by those enzymes involved in the utilization of preformed pyrimidines, this ribonucleotide affects the synthesis de novo of pyrimidines. Specifically, orotidylic acid decarboxylase, the final enzyme in the sequence responsible for the formation de novo of uridylic acid, is profoundly inhibited in a non-competitive fashion by azauridine-5'-phosphate, thereby restricting the supply of pyrimidine nucleotides in the affected cells.

A more intimate understanding of the mechanism of action of the various agents which influence nucleic acid metabolism not only will offer opportunities for establishing multiple or sequential metabolic blockades in malignant or parasitic cells, but also will permit detailed studies of the mechanisms of drug resistance, since the development of this condition very frequently limits the utility of otherwise effective agents. It may be hoped that these approaches will facilitate the rational design of new chemotherapeutic agents and provide a more fundamental understanding of the underlying disease processes.

5) Molecular Forces in Proteins of the Acetylcholine System and their Relationship to Drug Action

Dr. D. Nachmansohn

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Bioelectric currents conducting nerve impulses are associated with specific ion movements: Na ions enter the axon due to a specific several hundred-fold increase of permeability, followed by K efflux. The permeability change is effected by the action of acetylcholine (ACH) on the receptor protein; ACH-esterase rapidly inactivates the ester and restores the low Na-conductance. Analysis of the molecular forces in the active surface of the enzyme has helped the understanding of the action of drugs affecting the proteins of the ACH system. Relationships have been established between reactions of drugs with proteins in solution and events in intact cells.

The active surface of ACH-esterase is formed by 2 functionally and spatially separated subsites: an esteratic site at which a nucleophilic group forms a covalent bond with the carbon of the carbonyl group of the ester, and an anionic site attracting the cationic nitrogen group by Coulombic and van der Waals' forces, hereby orienting the substrate on the protein surface and greatly promoting the enzyme activity. In the first phase of the hydrolytic process an acetyl enzyme is formed under elimination of the alcohol, in the second the acetyl enzyme reacts with H_2O to form acetate and restored enzyme.

This analysis led to an explanation of the mechanism of action of organophosphorus compounds used as potential chemical warfare agents and as insecticides: the enzyme attacks the P atom in an S_N2 reaction; an acidic group is split off and a phosphorylated enzyme is formed. In contrast to the acetyl enzyme it does not react with H_2O and the enzyme is blocked; death ensues. Reactivation of the enzyme is possible by chemical reaction. Nucleophilic groups may attack the P atom and displace the phosphoryl group from the enzyme. If the nucleophilic group is attached to a cationic nitrogen group in the proper atomic distance, the attraction to the anionic site greatly promotes the reaction just as in the case of the physiological substrate. Among the structures, designed by Wilson, for obtaining the desired effect, 2-PAM turned out to be a particularly powerful reactivator of phosphorylated enzyme. Applied to animals it is an extremely potent antidote, especially in combination with atropine. In order to explain the extraordinary reactivating power, Wilson studied the "geography" of the enzyme and found that 2-PAM has a perfect complementary conformation to the phosphorylated enzyme.

Studies on the receptor provide another illustration of relationships between molecular forces of proteins acting in solution and in intact cells. When appropriate tertiary and quaternary methylated nitrogen derivatives are compared, the presence of an extra methyl group does not increase binding, but strongly promotes the enzyme activities (ACH-esterase and acetylase). The tetrahedral structure of the quaternary group suggests the folding of the protein around the

spherically shaped molecule. Experimental support for this assumption was obtained from studies of the entropy of activation. A comparable role of the extra methyl group in the receptor leading to a folding or unfolding of a small section of a protein chain could readily control ion movements by removing a strategically located positive charge repulsing Na. Evidence in this direction has been obtained in studies of the effect of methylated quaternary nitrogen derivatives and their tertiary analogs on the electrical activity of isolated electroplax. Certain quaternary compounds block conduction and simultaneously depolarize the membrane; they are receptor activators. Their tertiary analogs merely block but do not depolarize; they are receptor inhibitors. The special features required will be discussed.

The receptor protein has been isolated and identified by Ehrenpreis. Identification was achieved by comparing the strength of binding, tested by equilibrium dialysis, and the effectiveness on the electrical activity of a single isolated electroplax. A striking parallelism was obtained.

Replacing in ACH the methyl by a dodecyl group makes the molecule lipid-soluble. This and analogous structures rapidly and reversibly depolarize the membrane in low concentrations, 10^{-6} M or less. They produce muscular contraction in a completely curarized muscle, i.e., outside the synapse, by a direct action on the conducting membrane. Evidence has been offered for a specific action of these structures on the ACH system and for specific changes of ion permeability.

6) The Hemolytic State: Clinical and Biochemical Aspects of Primaquine-Sensitive Hemolysis

Dr. P. E. Carson and Dr. A. S. Alving

Department of Medicine,
University of Chicago, Chicago, Ill.

Acute intravascular hemolysis is induced in susceptible individuals when they ingest primaquine or other hemolytic agents such as nitrofurantoin, many sulfonamides, certain vitamin K derivatives, naphthalene and fava beans. Susceptibility is genetically determined and has been found in various ethnic groups of all races.

Administration of a standard dose of 30 mg. of primaquine daily to primaquine-sensitive but otherwise healthy male volunteers results in a self-limited hemolysis beginning in 3 to 4 days and lasting about 7 days. Recovery, with reticulocytosis, follows even if administration of primaquine is continued because the hemolysis is a function of cell age. The remaining and new erythrocytes are only relatively resistant to further hemolysis, however, since a second acute hemolysis can be induced by increasing the dose of primaquine. The relative hemolytic effect of various drugs in sensitive individuals can be shown by comparison of erythrocytic Cr^{51} survival curves with those obtained using the standard dose.

The erythrocytes of sensitive males are characterized by biochemical abnormalities which include a low and unstable reduced glutathione content, deficient glucose-6-phosphate dehydrogenase (G-6-PD), increased activities of glutathione reductase and aldolase, and decreased activity of catalase. Oxidized triphosphopyridine and diphosphopyridine nucleotides (TPN and DPN) are increased, the reduced forms are decreased, but the total level of these coenzymes is normal. Measurement of these parameters during hemolysis has shown only the following changes: an initial fall of reduced glutathione and of catalase activity and a rise in G-6-PD activity. Glutathione and G-6-PD return rapidly to pre-drug values; catalase returns slowly. Expression of primaquine-sensitivity is much more variable in women than men; the best correlation of these parameters with in vivo hemolysis is with the relative activity of G-6-PD.

The key to the mechanism of primaquine hemolysis, and possibly of cellular aging, appears to be concerned with the stability of G-6-PD. Glucose-6-phosphate dehydrogenase is inactivated by incubation with stromata in hemolyzates of primaquine-sensitive and non-sensitive erythrocytes alike. Kirkman (at the National Institutes of Health) has prepared purified G-6-PD, hemoglobin-free, from both kinds of erythrocytes. The enzyme appeared to be qualitatively identical, having the same Michaelis constants of 2.1×10^{-6} and 3.9×10^{-5} for TPN and glucose-6-phosphate, the same pH optimum curve from pH 6.0 to 10.0, and the same heat of activation, 9.5×10^{-3} cal/mole. He found the enzyme to be highly stabilized by TPN. We have found that, in hemolyzates, stromata inactivate G-6-PD by destroying bound TPN by their pyridine nucleotidase activity. Protection is given by TPN, DPN and nicotinamide. Protection by nicotinamide is indirect by interference with pyridine nucleotidase activity. Inactivation of G-6-PD in the absence of stromata is produced by adsorption of the pyridine nucleotides on activated charcoal. Nicotinamide offers no protection but TPN and DPN protect, the latter probably by enzymatic conversion to TPN.

Although the mechanism of maintaining the integrity of the erythrocyte through its normal life span in vivo remains unknown, the pattern of some of the essential factors is becoming more clear.

WORKSHOP SESSIONS

Monday, August 31, 1959 - 7:00 - 8:30 P.M.

One of the principal functions of the Society's Program Committee is to consider and bring to the membership special programs over and above the conventional 10-minute paper sessions. This year they have proposed as an experiment two informal workshop sessions in different areas of pharmacology.

The intent of these workshops is to make available to the advanced student of pharmacology and to those who have recently received their graduate degrees an opportunity to discuss specific areas of knowledge on an informal, but highly technical, basis with experts in those fields. Indeed, this type of communication is a privilege that simply has not been available to the younger investigator, who usually will not have had an opportunity or occasion to get to know outstanding men in the various fields under such optimal conditions. In order to keep these sessions on as informal a give-and-take basis as possible, attendance at each session will be limited to 15 qualified individuals who have registered for the sessions in advance. These sessions on "Clinical Pharmacology" and "Nature of Receptors" will run concurrently on Monday evening from 7:00 to 8:30 P.M.

The session on "Clinical Pharmacology" should be of particular interest, since it requires the unusual qualification of a sound knowledge of basic pharmacology and a good background of clinical medicine as well. The leaders for the discussion, Drs. Harry Gold, Carl Pfeiffer and Harry Beecher, are all outstanding investigators in their own right. Each represents a different field of specialization and a different point of view. Thus, one could expect an unusually stimulating discussion of the problems related to clinical experimental design, the interpretation of the results, pitfalls in this type of research, medicolegal aspects of such work, etc.

The session on "Nature of Receptors" is of an entirely different character and is one of the most fascinating and fundamental areas of pharmacology. Dr. Ullrich Trendelenburg and Dr. Robert Furchgott are unusually well qualified to handle such a session on this subject, which in effect is a key to all structure-activity relationships in pharmacology.

Since it is anticipated that the number of applicants for registration in these workshops will exceed substantially the limitations for enrollment, such applications will be handled on a first come basis among those who are qualified to attend.

ABSTRACTS

of Scientific Papers Presented at the
Fall Meeting
of the

AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, INC.

August 31 - September 3, 1959
University of Miami, Coral Gables, Florida

TUESDAY MORNING

CARDIOVASCULAR PHARMACOLOGY I
Chairman: M. DeV. Cotten Room N-202, Memorial Building

RESOLUTION OF INTERVAL-FORCE RELATIONSHIP OF HEART MUSCLE INTO NEGATIVE AND POSITIVE COMPONENTS. John R. Blinks (intr. by O. Krayer). Department of Pharmacology, Harvard Medical School, Boston.

The relationship of the force developed by heart muscle under steady-state conditions to the interval between contractions is strongly influenced by many factors. The curve describing this relationship may be resolved into two components, each of which describes an interval-dependent process. The two processes influence contractility in opposite directions. Differences in the interval-force relationship reflect differences in the relative importance of the two processes and in the frequency ranges over which they are operative. After a sudden change in interval, the influence of each process approaches its new level of importance at a characteristic rate. By virtue of differences in these rates, one may estimate the contribution of each process to the steady-state force achieved at any given frequency. The staircase phenomenon, post-stimulation potentiation, rest potentiation, post-extrasystolic potentiation, and the biphasic changes in force which often accompany frequency changes may all be accounted for on the basis of these two processes and their different rates of adaptation. (Supported by USPHS grants H-3738 and H-2205.)

DIRECT EFFECTS OF SYMPATHOMIMETIC AMINES AND DIGITALIS PREPARATIONS ON MYOCARDIAL CONTRACTILITY IN MAN. L. I. Goldberg, R. D. Bloodwell*, E. Braunwald* and A. G. Morrow*. National Heart Institute, Bethesda, Md.

Cardiac operations performed with the aid of cardiopulmonary bypass have provided the opportunity for the study of the direct effect of drugs on myocardial contractility in man. The Walton-Brodie strain gauge arch was sutured to the right ventricle of 30 patients undergoing such operations and continuous recordings of the isometric tension of this portion of the ventricle were made. Prior to perfusion, the comparative effects of sympathomimetic amines were studied in 15 patients. Both norepinephrine and epinephrine, in equivalent doses, produced pronounced increments in cardiac contractile force. Methoxamine, in equipressor doses, had little effect on the myocardium. Metaraminol and mephentermine caused sustained increases in contractility. Ten patients, without evidences of congestive heart failure, were acutely digitalized with acetyl-strophanthidin or lanatoside C during cardiopulmonary bypass. Marked increments in CF were noted within 5 minutes with acetyl-strophanthidin and within 10 minutes with lanatoside C. Peak effects were reached in about 20 minutes and persisted. This technic has also been found safe and practical in assessing the inotropic effects of other drugs, anesthetic agents, and methods employed during thoracic surgical operations.

EFFECTS OF LEVARTERENOL ON VENTRICULAR FORCE AND MYOCARDIAL O_2 CONSUMPTION DURING CARDIOPULMONARY BYPASS. E.E. Aldinger*, T.D. Darby, J.M. Tenney* and W.B. Thrower*. Depts. of Pharmacology and Surgery, Medical College of South Carolina, Charleston.

Total cardiopulmonary bypass was established in dogs using a Mark Kay-Cross type disc oxygenator and pump system for oxygenation of blood and total body perfusion. Ventricular contractile force (VCF), aortic pressure (BP) and venous pressure (VP) were recorded. Coronary flow (CF) was measured from a cannula placed in the isolated right ventricle. Arteriovenous O_2 differences were determined. Following a 5 minute control period during cardiopulmonary bypass, a levarterenol infusion was started into the venous reservoir of the pump. The following average increments above control occurred: VCF 200%, BP 100% and CF 200%. There was little change in VP. Although there was an increase in myocardial O_2 consumption, there was usually a decrease in A-V O_2 difference during the levarterenol infusion. The BP was lowered to control values by decreasing the total body perfusion rate. VCF remained 200% above control but CF decreased to only 100% above control levels. These results indicate that the vasopressor response to levarterenol is a major determinant of coronary blood flow. The positive inotropic effect appeared to be independent of coronary flow. (Supported by grants from American Heart Association and National Heart Institute)

THE MECHANISM OF ACTION OF OUABAIN. Kwang S. Lee, Dai H. Yu* and R. Burstein*. Dept. of Pharmacology, College of Medicine, State University of New York, Brooklyn, N.Y.

The oxygen consumption and the contractile tension of cat papillary muscles were measured simultaneously using the oxygen cathode and transducer method (Lee 1958). At the same time, concentrations of adenosinetriphosphate (ATP) and phosphocreatine (PC) were measured using the enzymatic method of Feinstein (1959). At the time when the contraction was increased maximally by ouabain, the oxygen consumption was somewhat increased, but concentrations of ATP and PC were slightly decreased. The toxic effect of ouabain, as manifested by the complete depression of contraction, was accompanied by a marked increase in QO_2 and considerable decrease in concentrations of ATP and PC. Muscles were "exhausted" by stimulating them electrically at a rate of 180/min. in a substrate free medium for 3 hours. The effects of various subtrates and ouabain on the oxygen consumption, contractility and concentrations of ATP and PC were investigated. The influence of ouabain on resting muscles without contraction were also studied. The analysis of the data suggests that the metabolic effect of ouabain is not the cause of the inotropic effect and vice versa. (Supported by a grant from the Nat. Inst. of Heart, U.S.P.H.S.)

FURTHER STUDIES ON THE POSITIVE INOTROPIC ACTION OF CONJUGATED CARBONYL COMPOUNDS. Thomas Baum*, Hector Vazquez-Leon* and Donald R. Bennett, Dept. of Pharmacology, Univ. of Michigan, Ann Arbor, Michigan.

A series of conjugated carbonyl compounds chemically related to the opened lactone ring of the cardiac glycosides have been shown to possess a positive inotropic effect on the hypodynamic cat papillary muscle preparation (J.P.E.T. 122: 480, 1958). Of the agents investigated in the dog and cat heart lung preparation, 3 have been found to be active. 3-acetylacrylic acid can be considered a representative of the active group. The dose of this compound required in the H.L.P. is 10^{-3}M, which is higher than is needed for stimulation of the papillary muscle. The use of blood as a medium for the papillary muscle likewise necessitates an increased drug concentration. The positive inotropic action of the active compounds, like that of the cardiac glycosides, is not prevented by dichloroisoproterenol or reserpinization of the animal. Unlike the glycosides, the active members do not depress A-V conduction or prolong the refractory period of Purkinje tissue in the anesthetized dog. **Supported by U.S.P.H.S. Grant #H-3945.**

QUINIDINE AND PROCAINE AMIDE ON CARDIAC CONTRACTILITY IN VIVO. E. T. Angelakos, E. P. Hastings and A. H. Hegnauer (intr. by E. R. Loew). Dept. of Physiology, Boston University School of Medicine, Boston, Massachusetts.

These classical antiarrhythmics are known to produce alterations in intracellular electrolyte composition which could affect myocardial contractility. A strain gauge arch was sutured on the left ventricular myocardium of dogs anesthetized with pentobarbital. Tension developed between the two points of attachment was measured with conventional recording methods. Both drugs exhibited a negative inotropic effect and altered the shape of the tension tracings. The peak contractile tension and the area under the tension curve were reduced. The former was taken as a measure of contractility. Single i.v. doses of less than 15 mg/kg of quinidine base (QB) and 10 mg/kg of procaine amide (PA) produced no significant effect. The submaximal dose-response range was between 10 and 30 mg/kg producing a depression of peak contractile tension from 85 to 55% the control values. Contractility of less than 50% of the control is not compatible with subsequent recovery. On a weight basis the degree of depression is essentially the same for both drugs. However in therapeutic dose levels the negative inotropic effect of PA is more severe than that of QB. Nevertheless equal amounts of the two drugs showed a more prolonged effect with QB than with PA.

POTENTIATION OF CARDIOACTIVE DRUGS BY GANGLIONIC BLOCKING AGENTS. Bert K.B. Lum and Perry L. Rashleigh (intr. by R.E. Green). Dept. of Pharmacology, Kansas Univ. Medical School, Kansas City, Kansas.

We have previously reported that tetraethylammonium and mecamylamine will act directly on vascular tissue to augment the responses to a variety of vasoactive drugs, thus demonstrating a potentiating action of these agents which is independent of ganglionic blockade (Lum and Rashleigh, Abstracts, Fall Meeting, Am. Soc. Pharmacol. & Exper. Therap., 1958,p. 23). In the present studies, experiments were performed to determine whether ganglionic blocking agents will act directly on cardiac tissue to augment the responses to cardioactive drugs. Mecamylamine potentiated the positive inotropic responses of the isolated cat auricle to a variety of agents including aminophylline, epinephrine, ephedrine, amphetamine, isoproterenol, norepinephrine, tyramine and cobefrine. Methantheline potentiated the inotropic responses of the cat auricle to epinephrine, norepinephrine and isoproterenol and inhibited or did not modify the responses to aminophylline, ephedrine, amphetamine and tyramine. Tetraethylammonium, hexamethonium, pentolinium and chlorisondamine did not potentiate the responses of the cat auricle to epinephrine.

(This investigation was supported by a PHS research grant #H-3762, from the National Heart Institute, Public Health Service).

PSYCHOPHARMACOLOGY I

Beaumont Lecture Hall, Memorial Building

EPINEPHRINE, NOREPINEPHRINE AND ACETYLCHOLINE AS CONDITIONED STIMULI FOR AVOIDANCE BEHAVIOR IN DOGS. Leonard Cook, Roger T. Kelleher*, Sanford P. Sher*, Arnold Davidson*, Research and Development Division, Smith Kline and French Laboratories, Philadelphia, Pa.

Studies were conducted to determine whether the effects of rapid injections of l-epinephrine, l-norepinephrine or acetylcholine might be employed as conditioned stimuli for eliciting conditioned avoidance responses in dogs. A brief electric shock which produced a leg-lift response (unconditioned response) was applied at 30 seconds after each injection. This time interval was determined on the basis of analysis of various monitored autonomic responses. Each drug injection was reinforced with an electric shock until conditioned avoidance leg-lift responses were consistently elicited by the drug injection alone. It was found that the effects of either l-epinephrine (10 gamma/kg.), l-norepinephrine (10 gamma/kg.), or acetylcholine (20 gamma/kg.) came to serve as conditioned stimuli after an appropriate number of training trials. It was found that when slight pressure, applied to Thiry-Vella jejunal loops in dogs, was reinforced with shock, this also came to serve as a conditioned stimulus for avoidance responses. These studies indicate that the effects of injections of l-epinephrine, l-norepinephrine or acetylcholine, as well as slight jejunal pressure, can play a role in the development and maintenance of conditioned avoidance behavior.

EFFECTS OF CHLORPROMAZINE, MEPROBAMATE, D-AMPHETAMINE, MEPHENESIN, OR PHENOBARBITAL ON TIME DISCRIMINATION IN RATS. Roger T. Kelleher* and Leonard Cook, Research and Development Division, Smith Kline and French Laboratories, Phila., Pa.

Hungry rats received food rewards only for those lever-pressing responses which occurred between 18 and 21 seconds after a preceding response. The relative frequencies of the times between responses (inter-response times) were computed; 80% of the responses occurred between 15 and 21 seconds apart. Chlorpromazine (2.5 - 5 mg/kg, p.o.) produced more long inter-response times even though stable response rates were maintained. Meprobamate (25 - 100 mg/kg, p.o.) or d-amphetamine (0.75 - 3 mg/kg, p.o.) produced more short inter-response times, and the total number of responses was markedly increased. Mephenesin (100 - 400 mg/kg, p.o.) or phenobarbital (10 - 40 mg/kg, p.o.) also produced more short inter-response times; however, both drugs decreased response rates because of periods in which all responding was depressed. Chlorpromazine, meprobamate, mephenesin, or phenobarbital did not affect behavior on a 50-response fixed-ratio schedule at doses which affected the inter-response time distribution on the preceding schedule; however, d-amphetamine depressed response rates on the fixed-ratio schedule.

IMPAIRMENT BY NITROUS OXIDE OF A COMPLEX DISCRIMINATION TASK IN MONKEYS. Murray E. Jarvik and Martin W. Adler*, Dept. of Pharmacology, Albert Einstein College of Med., New York City.

In the course of an investigation of the effects of drugs on a visual discrimination and delayed response test in monkeys, an 80:20 nitrous oxide - oxygen mixture was administered for ten minutes with comparable control periods. Head movements were measured at the same time. At this concentration, none of the animals lost consciousness and by gross observation, appeared to be normal. The gas mixture was fed into a plastic hood containing a contact movement device placed against the monkey's head as he sat in a specially designed chair. There was a marked depression in accuracy of performance by the animals on both tasks ranging from 23 to 59%. Premature responses and mature perseverative errors both increased. Changes in total responses and head movements due to nitrous oxide were independent of each other and showed increased variability. These effects differed from those of chlorpromazine, pentobarbital and amphetamine. (Fed. Proc., 18:362, 1959).

A QUANTITATIVE STUDY OF DISTORTION OF JUDGMENT PRODUCED BY DRUGS. Henry K. Beecher and Gene M. Smith*. Anesthesia Laboratory, Harvard Med. School, Boston, Mass.

A recently completed investigation in this laboratory showed that trained swimmers, runners and weight throwers in best condition perform significantly better two to three hours after receiving amphetamine than after a placebo. The present report concerns the subjective evaluations of these same athletes on the effects of amphetamine, secobarbital and placebo on their performance. Six groups of subjects were studied with a total sample of 57 athletes and 781 performances. After each performance the subject was asked to indicate whether he thought the medication he received that day had improved, retarded, or not affected his performance. The objective findings already reported indicated that approximately 75% of the athletes performed better under amphetamine than under placebo. After each event, but before being told his performance time, each subject was asked to judge how he had performed. The results showed that the subjects tended to under-value their performances under amphetamine and tended to over-value their performances under secobarbital. These differences were statistically significant. The errors in judgment were considerably greater when subjects performed alone than when they were in competition with one or two others. This provides a quantitative study of distortion of judgment produced by drugs.

A METHOD FOR MEASURING EFFECTS OF DRUGS ON VISUAL DISCRIMINATION IN THE CAT. Charles D. Hendley, May-I Chow and Francis Mechner (intr. by Martin M. Winbury). Dept. of Pharmacology, Schering Corp., Bloomfield, N.J.

In an operant conditioning box, cats are trained to press a lever for milk reinforcement. When an 8/sec. flickering light is on, the first response following the end of a variable time interval is reinforced, and turns the light off. During the subsequent dark period, no reward is possible. Four measures are calculated: latency to the first response in the light, response rate in light (L rate) and dark (D rate) and the discrimination ratio (L rate — D rate/L rate) (DR). Thirsted cats are run for an hour each day, 4-6 control runs per week and 1-2 with drug. Results to date have shown that certain phenothiazine tranquilizers cause a fall in DR at doses comparable to those used clinically. For example, 0.2-0.5 mg./kg. of perphenazine, p.o., produced a fall in DR of 20% or more. L rate usually decreased, latency increased, and the cats tended to stop working before the end of the hour. In some cases L rate was maintained even though discrimination was impaired. With some agents these effects were seen at doses which showed no change in behavior by standardized observational techniques. Other CNS depressants, or CNS stimulants in overdosage, impaired performance only at doses which showed gross behavioral effects. We conclude that certain phenothiazine tranquilizers influence this measure of visual discrimination at doses comparable to those used in man for the treatment of psychosis.

COMPARATIVE POTENCY OF PHENOTHIAZINE TRANQUILIZERS IN SUPPRESSING AVOIDANCE AND LOCOMOTOR BEHAVIOR: ITS IMPLICATIONS. Samuel Irwin. Dept. of Pharmacology, Schering Corp., Bloomfield, N.J.

The relative suppressant potencies of 8 phenothiazine tranquilizers on conditioned avoidance behavior (hurdle-jump) and locomotor activity (revolving treadwheel) were evaluated in 480 female, Charles River rats. With the exception of promazine, which was relatively ineffective in suppressing avoidance behavior, equivalent avoidance suppressing doses of all agents were equally effective in suppressing locomotor activity. Their relative subcutaneous potencies, in decreasing order, were: fluphenazine (Sch 6894) 72, trifluoperazine 25, perphenazine 23, thiopropazate 22, triflupromazine 6, prochlorperazine 5, chlorpromazine 1 and promazine <0.06. Acute tolerance development to the avoidance suppressant actions also was noted, e.g., chlorpromazine 58%, perphenazine 28%. If one compares the above data with clinical anti-psychotic efficacy, one finds fairly good correlation with the sequence but not with the relative potency of the values listed. In addition, the more potent anti-psychotics, such as fluphenazine (Sch 6894) and trifluoperazine, clinically produce almost no locomotor depression in effective dosage and may actually stimulate. Since all the phenothiazines tested, in equivalent dosage, produced equal suppression of avoidance and locomotor behavior, it seems unlikely that these measures are relevant to the "anti-psychotic" action of the drugs.

FLUOROBENZOYLPROPYLCHLOROPHENYLHYDROXYPIPERADINE (R-1625): PRELIMINARY CLINICAL EVALUATION AS AN ATARACTIC AGENT IN CLINIC PATIENTS WITH PSYCHOSOMATIC PROBLEMS. John H. Nodine*, Tibor Bodi*, Howard A. Levy* and John H. Moyer. Dept. of Medicine, Hahnemann Med. College and Hospital. Philadelphia, Pa.

A group of 32 patients in the Medical Clinic were given a complete history and physical examination, as well as basic laboratory studies and indicated consultations. Patients with predominantly psychiatric or psychosomatic symptoms were referred to a special team of internists and psychiatrists who saw the patients weekly or biweekly. An initial dose of 0.25 mgm. b.i.d. was used and was raised in successive increments to 2 mgm. q.i.d. depending upon the clinical response and side effects. Patients were calmed generally but remained alert mentally. Muscle-relaxing and neurologic side effects were the limiting factor in further elevation of the dose. Patients were followed with blood counts, urinalyses and liver function studies at regular intervals. No serious untoward reactions occurred.

THE EFFECT OF 4-(1-METHYL-3 INDOLYLETHYL) PYRIDINE HYDROCHLORIDE IN AMBULATORY PATIENTS WITH PSYCHONEUROSIS. Tibor Rodi, Howard A. Levy, and John H. Nodine (intr. by John H.Moyer) Dept. of Medicine, Hahnemann Med. College and Hospital, Philadelphia, Pa.

A group of 35 patients in the Medical Clinic were given a complete history and physical examination, as well as basic laboratory studies and indicated special examinations. Patients with predominantly psychiatric or psychosomatic symptoms were referred to a special team. Treatment was begun with 50 mg. three times daily and raised consecutively to 300 mg. three times daily, depending upon clinical response and side effects. Sleepiness was noted on several occasions, and several patients with mild hypertension became normotensive. It was concluded that the compound had a moderate central nervous system depressant activity and is beneficial in the therapy of psychoneurosis. Routine blood counts, urine analyses and liver function studies performed at regular intervals remained within normal limits.

STRUCTURE-ACTIVITY RELATIONS OF TRANQUILIZERS AND OF ANTI-CONVULSANTS SHOWN BY EFFECTS ON BEHAVIOR OF ISOLATED MICE. T.C. Barnes. Dept. of Pharmacology, Hahnemann Medical College, Philadelphia, Pa.

Previous reports (Barnes, J. Gen. Psychol. 25:249,1941; J. Pharmacol.Exp.Therap. 122:4A,1958; Fed.Proceed. 18:365,1959) have described the effect of solitary confinement on animals. Mice were isolated visually and each received a series of drugs to test effect on tactile head twitch and convulsive movements. Data are based on peak effects (below toxic level). Promazine (Ursprungssubstanz of Phenothiazines) had less than one-third the tranquilizing action of Chlorpromazine. Likewise Phenergan was weak. Trifluoperazine was 3 times as effective on head twitch as Chlorpromazine but produced no sedation. Lilly 26125, 8-ethoxy-2-butyl-amino-methyl-1, 4-benzodiexane with adrenolytic structure, tranquilized 45% of the mice compared with 70% for Chlorpromazine, but Dibenzaline was inactive. Acetozoleamide but not Chlorothiazide inhibited head twitch. Glutamic acid with closed structure tranquilized 11% and was anticonvulsant in 58% of animals but parent substance was inactive. Azocyclonol and Meprobamate tranquilized 17% and 11% of mice. Phenobarbital increased head twitch but reduced phenobarbital did not. Dilantin increased convulsive movements but the ethyl congener Peganone and reduced Dilantin were anticonvulsant. Isolated animals like isolated cells may provide new problems. The method eliminates the artifacts of electroshock in conditioning and in anticonvulsive studies.

KIDNEY AND ELECTROLYTES
Room N-205, Memorial Building

RENAL EXCRETORY PATTERN OF CHLORAMPHENICOL IN THE DOG. Teruo Takasu (Intr. by Duncan E. Hutcheon). Dept. of Medicine, Seton Hall College of Medicine and Dentistry, Jersey City, New Jersey.

The renal excretory pattern of chloramphenicol in the adult female dog was studied by the stop-flow method of Malvin and Wilde (The Physiologist, 1; 58, 1957). The unaltered chloramphenicol was found to be filtered through the glomeruli then reabsorbed continuously by the tubules up to the segment just proximal to the locus of distal sodium reabsorption. The U/P ratio always remained higher than 1.0. This indicates that tubular reabsorption of a biologically active chloramphenicol is probably a passive process resulting from a concentration gradient. A glucuronic acid conjugate of chloramphenicol was secreted by the proximal tubule at the locus of glucose reabsorption. These observations, therefore, confirmed Glasko's assumption (J. Pharmacol. & Exper. Therap., 96: 445, 1949). The distribution of chloramphenicol in the renal cortex and successive zones of the medulla will be discussed in relation to the above findings.
This study was supported by a research grant from Parke, Davis & Company.

RELATIVE DIURETIC EFFICACY OF DIURIL AND MERCUHYDRIN IN CONGESTIVE FAILURE. Nathaniel T. Kwit, Harry Gold, John H. Hughes,* Argyrios Golfinos* and Elizabeth A. Goessel.* Dept. of Pharmacology, Cornell University Med. College, Hospital for Joint Diseases and Beth Israel Hospital, New York.

In a recent report we described a method for comparing the efficacy of diuretic agents in bed patients in congestive failure under constant conditions of diet, in terms of the maximal diuretic potentiality of each drug. The measured response is the 24-hour weight loss after a dose as the most revealing and stable index of the action in clearing edema. The data are the paired comparisons of the responses, suitable for analysis in terms of ratios with confidence limits and in terms of signs with the sign test for significance. Uniformity tests comparing Mercuhydrin against itself show very close agreement between the assay values and the expected values. The method has now been applied to several oral diuretics. The results with Diuril fail to support the prevailing belief that it equals or closely approaches the diuretic efficacy of the intramuscular organic mercurial, and show further that its therapeutic efficacy lies in the range of two other oral diuretics we tested, which are now in common use.

EFFECT OF HYDROXYZINE (ATARAX) ON URINE FLOW AND RENAL HEMODYNAMICS. William P. Blackmore. Dept. of Pharmacology, U. of Texas Southwestern Med. School, Dallas, Texas.

Isolated observations have indicated that hydroxyzine may have an effect on decreasing urine flow. Therefore, a study was instituted to determine the effect, if any, of hydroxyzine on the kidney. Trained unanesthetized dogs were used in all experiments. Hydroxyzine was administered in a dose of 5 mg/kg. Oral administration of the compound to animals housed in metabolism cages where urine was collected for 3 hours showed that these dogs excreted an average of 73% of the water load as compared to control dogs which excreted 96% of the water load. Renal clearance experiments where hydroxyzine was infused for 30 minutes showed no change in glomerular filtration rate, renal plasma flow or electrolyte excretion. However, 1 and 2 hours following cessation of hydroxyzine a significant decrease in urine flow occurred which was manifested by a decrease in free water clearance with no change in osmolar clearance. In animals that had control urine flows below 2 ml/min. an antidiuresis was not noted. The results obtained indicate that hydroxzine does have an antidiuretic action. The possible mechanism of action will be discussed.

RELATION BETWEEN AMOUNT OF EDEMA AND RESPONSE TO A DIURETIC BY PATIENTS IN CONGESTIVE FAILURE. Harry Gold, Nathaniel T. Kwit, Argyrios Golfinos* and Elizabeth A. Goessel*. Dept. of Pharmacology, Cornell University Med. College, Hospital for Joint Diseases and Beth Israel Hospital, New York.

The belief prevails that the response to a dose of a diuretic depends among other things on the amount of available edema. In the course of another study, we found that in patients with abundant edema there is no relation between the amount of edema and the response per dose between patients, and that within patients, while the response per dose usually falls off as the edema diminishes with a succession of doses, this correlation does not depend on the quantity of edema per se, but on other factors, among them an anti-diuretic reaction to a diuretic challenge (D-AD), the algebraic sum of the two being reflected in the manifest diuretic response. This report shows some of the characteristics of the D-AD phenomenon. By means of an adrenal steroid blocking agent, it is shown that the adrenal participates in the anti-diuretic "alarm" reaction to a challenge to homeostasis by a diuretic in patients in congestive failure.

RENAL INTERACTIONS OF DRUGS AFFECTING URATE EXCRETION IN MAN. T.F. Yü and A.B. Gutman*. Departments of Medicine, Mt. Sinai Hospital and College of Physicians and Surgeons, Columbia University, New York, New York.

Renal excretion of urate in man is increased by probenecid, sulfinpyrazone and zoxazolamine; decreased by pyrazinamide and lactate; and increased by large doses and decreased by small doses of salicylate, phenylbutazone and its metabolite I. Any 2 uricosuric drugs given together are uricosuric (additive or substitutive). Any 2 drugs causing urate retention are substitutive when given together. Combining a uricosuric drug with one causing urate retention also results in an additive effect in the sense that uricosuria is suppressed.

These responses can be explained by recent studies indicating that the plasma urate filtered at the glomerulus is virtually completely reabsorbed by the tubules, and that the excreted urate ordinarily is derived by tubular secretion. Uricosuric drugs inhibit tubular reabsorption of urate; drugs that cause urate retention apparently inhibit tubular secretion of urate; salicylate, phenylbutazone and metabolite I apparently may do both, depending upon dosage. The additive or suppressive effects of various drug combinations can be explained by inhibition of tubular reabsorption, or inhibition of tubular secretion, or inhibition of both tubular transport systems simultaneously.

RENAL AND HYPOCHOLESTEROLEMIC EFFECTS OF BENZMALECENE IN DOGS. John E. Baer,* Horace F. Russo,* Antonia V. Brooks* and Karl H. Beyer. Merck Institute for Therapeutic Research, West Point, Pa.

Benzmalecene, N-(1-methyl-2,3-di-p-chlorophenylpropyl)-maleamic acid, is 7 to 10 times as effective as probenecid in inhibiting the renal tubular secretion of benzylpenicillin in the dog. The agent appears to be qualitatively similar to, but quantitatively more potent than, probenecid with respect to influence on uric acid transport in the mongrel and in the Dalmatian (Beyer et al., Am. J. Physiol., 166: 625, 1951). The daily oral administration of benzmalecene at 50 mg./kg. produced a prompt decrease of approximately 30 mg./100 ml. in the plasma cholesterol level of dogs maintained on a normal diet, apparently as a consequence of an inhibition of cholesterol biosynthesis from acetate and mevalonate that is displayed by benzmalecene in vitro (J. W. Huff and J. L. Gilfillan, Proc. Soc., in press). Benzmalecene has potent and specific activity in the biochemical processes responsible for the above effects, but shows no activity in autonomic, cardiovascular, or such other classic pharmacodynamic tests as have been examined.

DIURETIC ACTIVITY OF BENZTHIAZIDE DERIVATIVES. A. Scriabine*, J. McManus*, D. McKersie*, W. McLamore* and S. Y. P'an. Research Division, Chas. Pfizer and Co., Inc., Groton, Conn.

Several derivatives of benzthiazide, 3-benzylthiomethyl-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide, were found to cause a marked increase in the excretion of water, Na^+ and Cl^- when given orally to rats loaded with saline, 25 mg/kg. The compounds were tested at three dose levels and compared with benzthiazide in each assay. Changes in activity due to different substitutions in 3 and 6-positions of the heterocyclic ring will be discussed. Hydrobenzthiazide and other dihydro derivatives were found to be potent diuretic and saluretic agents. In rats, hydrobenzthiazide was more potent than benzthiazide. The difference in activity between benzthiazide and hydrobenzthiazide was, however, not as great as that between chlorothiazide and hydrochlorothiazide.

The activity of some benzthiazide derivatives was also studied in dogs by oral and intravenous administration. Pronounced diuretic and saluretic effects of these compounds were confirmed in this species.

THE DIURETIC ACTIVITY OF BENZTHIAZIDE. S. Y. P'an, A. Scriabine*.and D. McKersie*. Dept. of Macrobiology, Research Division, Chas. Pfizer and Co., Inc., Groton, Conn.

Benzthiazide, 3-benzylthiomethyl-6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide, is one of a series of substituted benzothiadiazines which possesses potent diuretic and saluretic effects. It is 7 and 16 times more potent than chlorothiazide in dogs and rats respectively in increasing sodium excretion. Marked diuretic and saluretic responses were obtained in dogs after an oral dose of 0.05 mg/kg and intravenous dose of 0.025 mg/kg. The electrolyte excretion was characterized by elimination of equimolar quantities of sodium and chloride. Potassium excretion was unaltered at these dose levels. Repeated daily oral administration of benzthiazide to dogs in doses of 250 to 1,000 mg/kg/day for 4 weeks did not cause a significant shift of plasma electrolytes. The diuretic and saluretic potencies of benzthiazide relative to hydrochlorothiazide will also be discussed.

DIURETIC ACTIVITY OF SOME 3-SUBSTITUTED 3,4-DIHYDRO-1,2,4-BENZOTHIADIAZINES. Richard M. Taylor* and Martin M. Winbury. Dept. of Pharmacology, Schering Corp., Bloomfield, N. J.

The diuretic activity of a group of 3-alkyl and 3-aralkyl derivatives of 6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide (hydrochlorothiazide) was investigated. Urine output and electrolyte excretion rates were determined following i.v. administration of small doses to dogs and oral administration to rats and dogs. The parent substance was used as a standard in all experiments. In general, it was found that the addition of small alkyl groups on the 3 position increased the natriuretic activity following oral and i.v. administration. Likewise, the addition of benzyl and substituted benzyl radicals on this position was accompanied by increased natriuresis after i.v. administration. However, in some cases, the latter compounds were considerably less active after oral administration, suggesting either poor absorption or destruction in the gastro-intestinal tract or liver. In addition, diuretic profiles of small doses of the benzyl compounds (10 mcgm./kgm., i.v.) show that these agents have a slower onset and a longer duration of action than the standard. Urinary electrolyte studies revealed that all compounds increased the excretion of sodium and chloride in approximately equimolar amounts. There appeared to be no correlation between diuretic potency and in vitro carbonic anhydrase inhibition activity in these groups of compounds.

EVALUATION OF DIURETIC ACTIVITY OF FOUR THIAZIDE DERIVATIVES. Morton Fuchs,* Sanford R. Mallin* and John H. Moyer. Dept. of Medicine, Hahnemann Medical College and Hospital, Phila., Pa.

Three new thiazide derivatives, flumethiazide, hydrochlorothiazide and hydroflumethiazide have been evaluated by us and compared clinically and pharmacologically with chlorothiazide. Bioassay studies have been used to determine dose response curves and comparative potency estimations. Statistical analysis of sodium and chloride excretion shows an effective dose range of 250 mgm to 2000 mgm for chlorothiazide and flumethiazide, 25 mgm to 200 mgm for hydrochlorothiazide and 25 mgm to 400 mgm for hydroflumethiazide. The natriuretic potency of these drugs at their optimal dose is essentially the same. Chloruresis is less than natriuresis with chlorothiazide and flumethiazide but exceeds sodium excretion following hydrochlorothiazide and hydroflumethiazide administration. Potassium excretion however, does not rise proportionately with larger doses, particularly with flumethiazide and hydroflumethiazide. Potency estimations and dose response curves were also obtained by measuring the 48 hour weight loss of edematous patients at varying doses of the drugs. These correlated well with sodium loss in the bioassay studies. Renal function studies showed no significant change in glomerular filtration rate or renal plasma flow. Chronic drug administration to edematous patients showed continuing effectiveness of these agents, whose diuretic activity is dependent on inhibition of renal tubular reabsorption.

EFFECTS OF BICARBONATE AND OF CHLORTHIAZIDE ON POTASSIUM EXCRETION IN SALT DEPLETED DOGS. Ora Rosen*, Joseph Hartog*, Helen M. Anderson*, John Laragh* and Paul Brazeau. Department of Medicine, Columbia University and Department of Pharmacology Albert Einstein College of Medicine, New York City.

Trained unanesthetized dogs receiving oral KCl (10gms daily) were given infusions of KCL (0.45 mEq/min) for 220 minutes. Chlorothiazide was given at the end of 160 minutes (2mg/kg i.v. and 3 mg/kg/hr added to the subsequent infusion). These experiments were then repeated in the same dogs with $KHCO_3$ instead of KCl infusions; then both experiments were repeated in each dog after mild salt depletion (peritoneal dialysis). The rate of K excretion was similar in all experiments before chlorothiazide and in all experiments an immediate rise of 100 to 250 uEq/min followed the administration of the drug. However, the abnormally high plasma K values seen in salt depleted dogs receiving KCl were much reduced in the depleted dogs receiving $KHCO_3$. Low rates of Na excretion were seen in the depleted dogs. Na excretion in those receiving KCl rose very little after chlorothiazide, but responded more like the normals when $KHCO_3$ was given. The anion infused was predominantly excreted throughout each experiment. After chlorothiazide, the absolute rates of Cl and HCO_3 excretion increased, but the ratio was little altered.

EFFECTS OF CERTAIN DRUGS AND METABOLIC ALTERATIONS ON NASAL SALT OUTPUT IN SEAGULLS. Bohdan R. Nechay*, James L. Larimer* and Thomas H. Maren. Department of Pharmacology and Therapeutics, University of Florida College of Medicine, Gainesville; and Department of Zoology, Duke University, Durham, N. C.

Nasal gland secretion in seagulls was established by i.v. infusion of 360 μM NaCl/kg/min. for 65-80 min., and samples were collected during two 30 min. periods, before and after drugs. Secretion of untreated birds showed: pH 6.9-7.2; CO_2 8-13 mM/l; K^+ 30-60 mM/l; Cl^- and Na^+ 700-900 mM/l. After drugs composition remained unchanged except for CO_2 and pH. Volumes of secretion were proportional to Cl^- excreted. Cl^- output in period before drug is assigned 100. Changes in second period were: no treatment, 137; carbonic anhydrase (C.A.) inhibition by methazolamide (4 mg/kg), 42, fluid became more alkaline; meralluride (3 mg/kg of Hg), 48; chlorothiazide (10 mg/kg), 110; HCl (10 mM/kg), 27, plasma pCO_2 was low and fluid became more alkaline; 'tris' buffer (12 mM/kg), 115; $NaHCO_3$ (12 mM/kg), 124, plasma pCO_2 was high. $NaHCO_3$ (12 mM/kg) but not HCl (5 mM/kg) blocked action of methazolamide.

Data suggest active transport of Cl^- (or Na^+) involving C.A. Enzyme was found in gland. Proposed mechanism: H^+ gradient dependent on pCO_2 somehow activates the transport system. C.A. inhibition acts at this step by reducing H^+ formation. Inhibition may be overcome if pCO_2 is high. Actual transport step is sensitive to meralluride but not chlorothiazide.

CELLULAR AND BIOCHEMICAL PHARMACOLOGY I
Room N-204, Memorial Building

FACTORS AFFECTING DRUG METABOLISM BY LIVER MICROSOMES. II: LIVER TUMORS. Richard H. Adamson*, Fernando Aleu*, and James R. Fouts. Depts. of Pharmacology and Pathology, State Univ. of Iowa, Iowa City.

A variety of drug metabolisms occurs in liver microsomes. Various physiological and pathological states affect microsomal structure. Thus, electron micrographs show marked structural changes in this subcellular fraction when neoplastic transformation occurs. These changes include an almost complete disappearance of that part of the microsomes with which the drug enzyme systems seem to be associated. This led us to compare the metabolism of drugs by normal liver vs. liver tumors. Various tumors were induced by feeding carcinogens such as butter yellow or acetylaminofluorene. In addition, a transplantable growth, the Novikoff hepatoma, was studied. Histological studies of the masses so produced will be presented. In every case yet examined, the neoplastic process is characterized by a loss of all the drug metabolisms studied. This loss of metabolism is apparently due to a lack of the enzyme systems and not to a deficiency in cofactors such as TPNH. The effects of drugs in animals bearing liver tumors will also be presented. The differences in drug metabolism in normal vs. liver tumor-bearing animals are of importance in the use of drugs in animals with such tumors and to the design of therapeutic agents for use against such growths. Supported by a grant from the Iowa Division of the American Cancer Society.

FACTORS AFFECTING DRUG METABOLISM BY LIVER MICROSOMES. III: JAUNDICE. Edwin McLuen*, Fernando Aleu*, and James R. Fouts. Depts. Pharmacology and Pathology, State Univ. of Iowa, Iowa City.

Microsomal ultra-structure changes in a number of pathological states. Other workers have noted that deoxycholate dissolves that part of the microsomes with which the drug enzyme systems are thought to be associated. This led to our study of the effects of obstructive jaundice on drug metabolism. The jaundice was induced in rabbits by ligation of the cystic and common bile ducts. Livers were assayed for the various drug enzyme systems at various times after surgery. Samples of these livers were also examined histologically. Effects of drugs such as hexobarbital, known to be metabolized in liver microsomes, were studied in vivo in jaundiced vs. normal rabbits, e.g., by using sleeping times. Results indicate that jaundice of longer than 1 week duration is characterized by marked sensitivity of the animal to drugs in vivo and an almost complete loss of liver microsomal metabolism in vitro. Jaundice of less than 1 week duration leads to less marked effects of qualitatively similar character. The marked depression of drug metabolism is apparently due to an effect on the enzyme system and not to any lack of cofactors such as TPNH. These findings have some bearing on the use of drugs in animals with such pathology. Supported by research grant RG-6034 from the U. S. Public Health Service.

A NEW ENZYMATIC ASSAY FOR ANALOGUES AND ANTIMETABOLITES OF TYROSINE AND PHENYLALANINE. Bert N. La Du and Patricia J. Michael (Intr. by Sidney Udenfriend). Natl. Inst. of Arthritis and Metabolic Diseases, Bethesda, Maryland.

We have recently developed an enzymatic spectrophotometric method to determine L-phenylalanine in plasma. This method utilizes L-amino acid oxidase from snake venom to convert phenylalanine to phenylpyruvic acid. The absorption of the latter is measured in the ultraviolet. L-Tyrosine and L-tryptophan are also oxidized to their respective α-keto acids, and by taking advantage of the difference in the absorption spectra of the enol-borate complexes, the three amino acids can be determined simultaneously. In the course of these studies it was found that a number of analogues of phenylalanine and tyrosine which are also oxidized by L-amino oxidase to α-keto acids could likewise be measured as enol-borate complexes. Among the compounds which we found to be very active substrates with the oxidase and to yield complexes with sufficiently high molar extinction coefficients to permit analysis at low concentrations are: m-tyrosine, dibromotyrosine, p-fluorophenylalanine, 3-amino-tyrosine, monoiodotyrosine and mononitrotyrosine. β-2-Thienylalanine also gave a highly absorbing product. This method has been used to measure some of these compounds in plasma after their parenteral administration in guinea pigs and this data will be presented.

PHARMACOLOGICAL ACTIVITY OF O-METHYLTRANSFERASE (OMT) INHIBITORS. D.W. Wylie, S. Archer and A. Arnold (intro. by A.M. Lands). Sterling-Winthrop Research Institute, Rensselaer, NY.

The primary route of metabolism of epinephrine and norepinephrine is by methylation of the phenolic OH in the 3 position (Axelrod: Science 126: 400, 1957). Various polyphenols augment epinephrine effects on smooth muscle and on the theory that such substances were competitive substrates for OMT we studied their effects on this enzyme under in vitro conditions by the technique of Axelrod and Tomchick (J.B.C. 230: 702, 1958); pyrogallol was 20 times and gallic acid 10 times more active than catechol. In the spinal cat pyrogallol and catechol were more effective than gallic acid in augmenting epinephrine effects on the B.P. Luduena showed that the toxicity of i.v. epinephrine in rats was blocked by adrenolytics, indicating that it was due to sympathomimetic effects (Arch. int. Pharmacodyn. - in press). We have found that the intravenous toxicity of epinephrine and norepinephrine can be augmented twofold by simultaneous administration with 5 mg/kg catechol or 40 mg/kg pyrogallol, so that under in vivo conditions catechol is more active. It was found that 0.1 mg/kg cocaine equally increased epinephrine toxicity but was extremely weak as an inhibitor under in vitro conditions. The doses of the inhibitors used were without pressor effects in the cat and well below the i.v. LD_{50}'s in the rat.

VOLATILE AMINES IN BRAIN. Conrad G. Honegger and Ruth Honegger (intr. by Carl C. Pfeiffer) Dept. of Pharmacology, Emory University, Atlanta, Georgia.

Fresh pig brain (7.18 kg) was analyzed for volatile amine content. The procedure for isolation was as follows: ethanolic extract of brain homogenate was vacuum-steam distilled in saturated $Ba(OH)_2$ solution and the volatile amines collected in 1 normal HCl. This crude amine mixture was then separated by fractional vacuum-steam distillation and five fractions were collected at increasing temperatures (15 - 60°C). These fractions, which represent the free amine constituents, were evaporated to dryness, redissolved in an appropriate solvent and analyzed by gas-phase-chromatography, paper-electrophoresis and paper-chromatography. From these fractions fourteen different substances were detected. Two substances were identified as the known brain constituents ammonia and aminoethanol. The presence of 2-dimethylaminoethanol reported earlier was confirmed. We were able to identify five of the remaining substances as methylamine (230 µg/kg), dimethylamine (975 µg/kg), ethylamine (150 µg/kg), pyrrolidine (17 µg/kg) and piperidine (27µg/kg). The approximate quantities were determined from the dye-reaction on paper. The remaining six substances are as yet unidentified. Studies of the bound volatile amine content will also be presented.

APPEARANCE OF CERTAIN ONIUM COMPOUNDS IN BRAIN TISSUE FOLLOWING THEIR INTRAVENOUS ADMINISTRATION TO RATS. Ruth R. Levine. Dept. of Pharmacology and Experimental Therapeutics, Boston Univ. School of Medicine, Boston, Mass.

Some of the effects produced by quaternary ammonium agents following their intravenous injection are presumptive evidence that these compounds reach and have activity in the central nervous system. The actual presence of any of these onium compounds in brain tissue following parenteral administration, however, has not been demonstrated by chemical means. Using the bromphenol blue spectrophotometric method of Mitchell and Clark (Proc. Soc. Exptl. Biol. Med. 81:105, 1952), which is specific for onium cations, we have found significant amounts of hexamethonium (C6), hexamethylene bisdimethylsulfonium dibromide (DMS), hexamethylene bisdiethylsulfonium diiodide (DES) and N-(6-trimethylaminohexyl)-isoquinoline (IN 181) in rat brain tissue following injection into the saphenous vein. Following a dose of 30 mg/kg, DMS was found in brain within 30 minutes and the ratio of its concentration in blood and brain approached unity between 60-90 minutes. After 60 minutes, IN 181 (15 mg/kg) also was found in equal concentration in blood and brain. The mean brain/blood ratio for DES (75 mg/kg) was 0.15 at 60 minutes and for C6 (75 mg/kg given in divided doses) was 0.19 at 30 minutes. The passage of these compounds into the brain did not correlate with their lipoid solubilities.

A GENERAL THEORY FOR CHLORPROMAZINE ACTION
M. A. Spirtes and Paul S. Guth*. Dept. of Pharmacology Hahnemann Medical College, Philadelphia, Pa.

Evidence will be presented to demonstrate an effect of chlorpromazine on mitochondrial permeability. It can be calculated from the data of Salzman and Brodie and Wase, Christensen and Polley that a concentration of chlorpromazine sufficient to inhibit mitochondrial permeability is present in the hypothalamus. Chlorpromazine determinations by a modification of the ferric chloride method were performed on brain samples procured 15-30 minutes after intravenous injection of 10 milligrams per kilogram. This method does not determine chlorpromazine sulfoxide. Levels of approximately 10^{-4} Molar were found in the thalamus-hypothalamus region confirming the calculated data discussed above. The concentration of chlorpromazine in this region is usually 2-3 X that found in the rest of the brain. A general theory for the mode of action of chlorpromazine will be proposed based on the fact that most of the in vitro work done with this drug and certainly all in vivo work involves membrane-enclosed systems. It is assumed that chlorpromazine inhibits the permeability of all such systems. A discussion of the numerous and varied effects of this drug found in the literature will be presented from this point of view. The usefulness in therapy of this drug may then derive from a greater inhibition of permeability at one or more loci in the body.

THE EFFECT OF RESERPINE ON OXYGEN CONSUMPTION AND PROTEIN SYNTHESIS IN AN EXPERIMENTAL MOUSE TUMOR. William L. West*, Gordon M. Baird*, Jacequline D. Steward* and Sachindra N. Pradhan. Dept. of Pharmacology, Howard University College of Medicine, Washington, D. C.

A marked diminution in tumor volume was noted with a small dose of reserpine (1 microgram/gram daily for 2 or 3 days) and this tumor-inhibiting effect was unrelated to its depressant effect on the oxygen consumption in the intact animal (West and Pradhan: J. Pharmacol. Exp. Therap., 122, 83A, 1958).

In the present experiment, the mechanism of anti-tumor action of reserpine was further explored by studying its effect on oxygen consumption of a lymphosarcomatous tumor (L-1) and liver in CAF_1 mice, and on the incorporation of labeled amino acids in the protein fraction from these tissues. The L-1 tumor was used in both solid and ascites forms.

Reserpine was found to inhibit protein synthesis in both solid and ascites forms of tumor, but not in liver. It did not show any definite effect on oxygen consumption of tumor or liver tissue in vitro. (Supported by a research grant CY-2054 from the National Cancer Institute, Public Health Service).

FACTORS CONTROLLING PENETRATION OF L-ASCORBIC ACID INTO TISSUES. G. R. Martin* and J. J. Burns. National Heart Inst. Bethesda, Md.

L-Ascorbic acid-1-C^{14}, when administered intracardially in small doses (2 mg) to intact rats, is rapidly transferred from blood to tissues where oxidation or storage occurs. Nephrectomy, prior to administration of the labeled vitamin, causes a marked lag in its accumulation in tissues and in its subsequent metabolism. The ratio, tissue specific activity of ascorbic acid to serum specific activity (indicating approach of a tissue to equilibrium), was higher in intact than in nephrectomized animals at any given time in all cases tested. Administration of large doses of ascorbic acid (20 mg) to nephrectomized rats by intracardiac injection, or induction of accelerated ascorbic acid biosynthesis in such animals with Chloretone resulted in marked accumulation of the vitamin in serum without measureable tissue transfer. A similar amount of exogenous dehydroascorbic acid, the oxidized non-ionic form of the vitamin, was largely removed from the serum. The ascorbic acid in serum of blood drawn from the renal vein of dogs, rats and rabbits was primarily in the form of dehydroascorbic acid, whereas serum from the carotid artery, femoral and jugular veins was primarily in the reduced form. These findings suggest that ascorbic acid enters tissues as dehydroascorbic acid and that the kidney may play a role in the distribution of the vitamin by oxidizing it to the unionized, easily penetrable form.

GUIDE TO THE WORLD LITERATURE ON CARDIOVASCULAR AGENTS. Isaac D. Welt (intr. by Chauncey D. Leake). Div. Med. Sci., Nat. Acad. Sci.- Nat. Res. Council, Washington, D. C.

The Cardiovascular Literature Project was established (Res. Grant H-2045, Nat. Heart Inst.) in order to provide a comprehensive and detailed guide to the polyglot world literature dealing with the cardiovascular effects of chemical agents, published during the last three decades.

The first volume of the projected series, that covering the period 1951-55, will shortly become available and will cover the pertinent information contained in over 12,000 papers from some 375 journals. Drug names have been carefully standardized. Pharmacological effects are described under several hundred standard subject headings consisting of well-defined terms from anatomy, physiology, pharmacology and pathology, with numerous cross-references.

Index entries are informative, one or two-sentence annotations, compiled by some forty qualified medical scientists and physicians. Sufficient information is presented so that recourse to the original literature is frequently unnecessary.

It is hoped that the series of index-handbooks to be issued during the next few years will serve to further stimulate research in this important area by making its voluminous and widely-scattered literature more easily accessible.

ROUTINE DIRECT MEASUREMENT OF ARTERIAL PRESSURE IN UNANESTHETIZED RATS. James R. Weeks, Dept. of Pharmacology, The Upjohn Company, Kalamazoo, Mich.

Still et al. [J. Appl. Physiol. 8: 575 (1956)] described direct registration of blood pressure of unanesthetized rats by permanent intubation of the aorta with polyethylene tubes. In their method, small bore polyethylene tubing (PE 10) was inserted into the aorta, then passed out of the abdominal cavity and subcutaneously to an exit at the base of the neck. Since the end of the tubing was heat sealed and cut open, frequent routine measurements could not be obtained. To circumvent this limitation, we joined PE 10 to larger PE 50, passed it through the back muscles to the base of the neck where it was joined subcutaneously to a short piece of 22 ga. needle tubing, which then emerged just behind the ears. On this needle tubing was a short length of reinforced PE 50 (PE 160 jacketed) tubing plugged with a wire. This terminal piece could readily be replaced as necessary. Blood pressure was recorded using a Statham P23G pressure transducer. Simultaneous recording of blood pressure directly from the aorta and indirectly by the photoelectric tensometer showed that removing and replacing the cuff (Rosette and Handler type) often resulted in different apparent blood pressures. Also, there was no consistent relationship between direct and indirect blood pressure values. Rats so prepared have had pressures measured repeatedly for many weeks.

ON THE NATURE OF PLASMIN-INDUCED HYPOTENSION. N. Back. Sect. of Physiology and Pharmacology, Roswell Park Memorial Institute, Buffalo, N.Y.

Intravenous administration of plasmin into anesthetized dogs resulted in an immediate but temporary blood pressure fall. The hypotension was found to be proportional to the plasmin dose, and was not elicited by either plasminogen or streptokinase. Spontaneously-activated, and streptokinase-activated human plasmin as well as chloroform-activated bovine and dog plasmin exhibited this hypotensive property. Successive administrations of human plasmin within a short period of time resulted in a progressive diminution and eventual abolishment of the hypotensive response. Dogs thus rendered tachyphylactic to the hypotensive effect of human plasmin still responded to both dog and bovine plasmin. Pretreatment with atropine and antihistamines did not prevent the blood pressure fall. The role of plasma protein decomposition products resulting from plasmin action was studied in plasmaphoresed animals. In such animals, plasmin still evoked a hypotensive response. The possible contribution of a bradykinin-like vasodilator substance (kallidin) is suggested by the demonstration that dogs rendered tachyphylactic to the hypotensive effect of human urinary kallikrein no longer responded to a hypotensive dose of human plasmin. These vasodilator polypeptide substances will be discussed with regard to their possible involvement either as contaminants in the plasminogen preparation used or as byproducts formed in vivo by plasmin action.

ANTIPRESSOR ACTIONS OF SARRACENIACEAE (PITCHER PLANT FAMILY). Russell A. Waud and Roland K. Lee*. Dept. of Pharmacology, Univ. of Western Ontario Medical School, London, Canada.

Effects of extracts and crystalline powders prepared from the leaves were tested on dogs arranged for recording B. P., EKG., EEG and H.R., for perfusion of the isolated head (Heymans), and C.O. (Weese). Blood pressure, effects on ganglia supplying the nictitating membrane, blocked autonomic ganglia, and reactions to norepinephrine were studied in cats. The drug was administered I.V. in doses (representing dried powder) ranging from 10 to 50 mg./Kg. In both cats and dogs there was a precipitate fall in B.P., which was followed by a partial return and then a secondary fall, which persisted for 3½ to 4 hours. The heart rate rose and the C.O. fell during the initial fall in B.P. During the secondary fall the C.O. was increased considerably above normal. There was no initial fall in B.P. in the artificial heart-lung preparation. In the isolated head experiments there was a fall in B.P. in both dogs. This suggests both a central and a peripheral action. The drug had no effect on impulses passing from the cervical sympathetic to the nictitating membrane. Its action was not affected by hexamethonium, nor was it adrenolytic. There were no effects on the EKG or EEG. Isolated crystals were inactive.

Supported by National Research Council, Canada.

NASAL VOLUME AS A MEASUREMENT OF TACHYPHYLAXIS. Ernest A. Daigneault (Intr. by Richard P. White). Div. of Pharmacol., Univ. of Tenn. Med. Units, Memphis, Tennessee.

Winder et al. (Jour. Pharmacol. and Exp. Therap. 93:63, 1948) discussed in detail the problem of tachyphylaxis to phenethylamines. The systems they used to base their views were the dogs' neurally isolated mucosa and the blood pressure. One conclusion was that tachyphylaxis in a vigorously compensated system, as for blood pressure regulation, a return to normal is seen, whereas, in a noncompensating system as with the denervated nasal mucosa the pattern observed is a maximal dose-response. It was found, however, that the administration of d-amphetamine (0.367 mgm/kg) at twenty minute intervals caused a maximal dose-response without denervation of the nasal mucosa. Morever, atropinization and bilateral vagotomy did not change the maximal nasal volume obtained with d-amphetamine. Other sympathomimetic amines (metamphetamine, methoxamine and phenylpropanolamine) are to be similarly discussed. These experiments show that the existence of a maximal dose-response state in the nasal mucosa should not be interpreted as tachyphylaxis. (Supported by a grant from the Memphis Heart Association, Tenn.)

ACETAZOLEAMIDE AND THE VENOUS PRESSURE OF THE CAT EYE. Frank J. Macri. Ophthalmology Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Maryland.

It is known that systemically administered acetazoleamide lowers intraocular pressure. This action has been attributed to a decrease of aqueous humor formation resulting from carbonic anhydrase inhibition. No lowering of episcleral venous pressure has been reported. In a series of experiments on in situ and perfused enucleated cat eyes, the effect of acetazoleamide on the intraocular and venous pressures was studied. Under the conditions of these experiments, the venous pressure was observed to fall simultaneously with the intraocular pressure. In the living eye, the venous pressure fall was of the same magnitude as the intraocular pressure decrease. The venous outflow system of the cat and its relationship to the channels of aqueous humor outflow will be discussed. Correlations of intraocular and venous pressures before and after acetazoleamide administration will also be presented.

INDEPENDENCE OF CARDIAC & MOTOR ORIENTING REFLEXES: SCHIZOKINESIS. Joseph E.O. Newton* & W. Horsley Gantt. Pavlovian Laboratory, Johns Hopkins University & V.A. Hosp., Perry Pt., Md.

The orienting reflex (OR) consists of turning towards a novel stimulus, etc. Cardiac components of the OR, studied in this laboratory for 15 years, consist of cardiac acceleration 10-40 beats/min. Because reflex cardiac acceleration due to movement might be responsible for the cardiac OR, curare was administered to eliminate this factor. After 5-10 control presentations of a bell in 8 dogs, animal was paralyzed with 1.0 to 2.0 units d-tubocurarine chlorid, & while paralyzed subjected to 10 additional bells; there was skeletal paralysis & lack of spontaneous movements. Results: Strong motor OR's during control period were blocked completely by curare in 4 dogs, depressed in 4 others. Bell produced average cardiac acceleration of 22 beats/min. in control series; under curare, the same acceleration in 2 dogs, 50% decrease in 5, increase in one dog. Cardiac control OR's were 87% acceleratory, versus 83% acceleratory under drug (average of all dogs). All animals retained cardiac OR's under curare. Conclusions: The cardiac acceleratory component of the OR is not blocked by curare, therefore this response appears to be mainly the result of excitation in CNS instead of reflex effect of muscular movements.

MECHANISM OF CLOT LYSIS BY PLASMIN AND THE ROLE OF ANTIPLASMIN. Clara M. Ambrus, Nathan Back, and Julian L. Ambrus. Roswell Park Mem. Inst. and Dept. of Pharmacology, Univ. of Buffalo School of Med.

In clinical studies on the therapeutic use of plasmin in thrombo-embolic disorders, and in animal experiments with venous clots produced, using I^{131}-labeled fibrin, it was noticed that plasmin activity disappeared from the blood within an hour, yet no fibrinolysis was observed until 4-24 hours after treatment. Clots removed after disappearance of circulating fibrinolytic activity, progressed to lysis upon in vitro incubation. Radioactivity following intervenous infusion of I^{131}-labeled plasmin, persisted for several hours although fibrinolytic activity disappeared within one hour. Clots produced after disappearance of circulating fibrinolytic activity but before disappearance of radioactivity, exhibited lysis. Standard amounts of plasmin were mixed with various amounts of antiplasmin in vitro. Caseinolytic activity of the mixture disappeared at antiplasmin levels at which fibrinolytic activity was still present. It appears that infused plasmin rapidly complexes with antiplasmin. Fibrin can effectively compete with antiplasmin for plasmin. Other proteins are thus protected from proteolysis while plasmin is available in an inactive storage form for fibrinolysis whenever clots form.
(Supported by grants from Natl. Inst. of Health, U.S.P.H.S., Am. Heart Assoc., Parke Davis & Co. and Merck, Sharp & Dohme Co.)

EPINEPHRINE SECRETION AND DESTRUCTION DURING HEMORRHAGIC HYPOTENSION IN DOGS. Daniel T. Watts, James C. Meador* and Elizabeth L. Arnett.* Dept. of Pharmacology, West Virginia University Medical Center, Morgantown, W. Va.

Dogs under pentobarbital anesthesia were bled to a mean arterial pressure of 40 mm.Hg and the arterial blood epinephrine content estimated by bioassay (Am. J. Physiol. 184:271, 1956) at 6-10 minute intervals before and after acute adrenalectomy. Epinephrine levels for a typical experiment, expressed as micrograms/liter as the base were as follows: Before hemorrhage, <1; after bleeding to 40 mm.Hg, 17.5; after left adrenal removed, 12.3; after both adrenals removed <1 within 3 minutes. These data indicate that the epinephrine found in the peripheral circulation during hemorrhagic hypotension was liberated by the adrenal medulla. In other experiments, simultaneous femoral arterio-venous determinations of epinephrine showed that 68% of the endogenously liberated epinephrine was destroyed by passage through the leg under hypovolemic conditions at 40 mm.Hg arterial pressure. This compares favorably to 65% destruction of exogenously infused epinephrine (5 micrograms/kgm./min.) in the hind limb under normovolemic, hypertensive conditions. Thus the massive amounts of epinephrine observed in the blood during hemorrhagic shock are probably due to hypersecretion and not to decreased destruction by the tissues. (Supported in part by PHS Research Grant H-1684).

INFLUENCE OF MONAMINE OXIDASE INHIBITORS ON THE CARDIOVASCULAR EFFECTS OF SYMPATHOMIMETIC AMINES. J. Gatgounis*, L. I. Goldberg and W. G. Whitlock*. Dept. of Pharmacology, Medical College of South Carolina, Charleston and National Heart Institute, Bethesda, Md.

Prior administration of monamine oxidase inhibitors (MAO) potentiates the inotropic actions of dopamine, tryptamine and tyramine; norepinephrine and serotonin are not potentiated (Goldberg and Sjoerdsma, J.P.E.T. In Press). In the present study the effects of MAO inhibitors on the cardiovascular actions of a larger number of amines was determined in anesthetised, vagotomized dogs. The inotropic action of levarterenol, epinephrine, synephrine, phenyl propanolamine, hydroxyamphetamine, methamphetamine, amphetamine, isoproterenol, methoxamine and phenylephrine were not potentiated. The inotropic actions of dopamine, tryptamine, para and meta tyramine, Epinine, β-phenylethylamine were augmented. The results suggest that the presence of a hydroxyl group on the beta carbon or a methyl group on the alpha carbon prevents potentiation. This series is being extended. (Supported by grants from the National Heart Institute.)

NEUROPHARMACOLOGY I

Chairman: K. Unna Beaumont Lecture Hall, Memorial Building

THE EFFECT OF γ AMINOBUTYRIC ACID ON SYNAPTIC TRANSMISSION IN AUTONOMIC GANGLIA. R. J. Matthews and B. J. Roberts (intr. by M. J. Vander Brook). Dept. of Pharmacology, The Upjohn Company, Kalamazoo, Michigan.

The superior cervical and inferior mesenteric ganglia were studied in situ in the decerebrate cat. The preganglionic trunks were maximally stimulated once every two sec with rectangular pulses of 0.5 msec duration. The amplitude of the postganglionic spike potential served as the index of ganglionic transmission. No effect could be obtained in the superior cervical ganglion with γ aminobutyric acid (GABA) administered either intravenously in doses of 1 mg/kg or intra-arterially as high as 100 μg/kg. In the inferior mesenteric ganglion it was found necessary to administer GABA intra-arterially in doses of 100 μg/kg to produce a moderate decrease in the postganglionic response. In five experiments this dose caused a mean depression at maximum effect of 21% with a standard error of 5.4%. Recovery from depression was usually complete within three min. Complete block of ganglionic transmission was never observed even with doses of 1 mg/kg i.a. The depression was confined to the synapse since the amplitude of the through-conducted spike was unaltered. The sensitivity of the preparations varied widely and in 50% of the preparations the depression did not increase with an increase in dose. One preparation did not respond to GABA in doses up to 1 mg/kg.

THE EFFECTS OF γ-AMINOBUTYRIC ACID, γ-AMINOBUTYRYL CHOLINE, ATROPINE AND ESERINE ON EVOKED CORTICAL POTENTIALS. A. J. Hance,* P. Bach-y-Rita* and K. F. Killam. Depts. of Anatomy and Pharmacology, Univ. of Calif. Med. Ctr. at Los Angeles.

The possibility that γ-aminobutyrylcholine (GABCh) might be the active form of γ-aminobutyric acid (GABA) in the brain led to a comparative study of the action of these two substances on cortical potentials evoked by a variety of stimuli. The changes produced by GABA have been described previously by several workers and were confirmed in the present experiments. Intravenous GABCh (1-10 mgm/kgm) had little effect on the evoked cortical responses and failed to modify the action of topical applications of GABA to any great extent. Since it was possible that GABCh failed to pass the blood-brain barrier, it was applied topically in concentrations ranging from 0.1 to 5 %. At these concentrations little change in the cortical potentials was observed. Only in preparations in which GABCh had been administered intravenously and also applied topically was there a slight reduction in the amplitude of the negative phases of local cortical, trans-callosal and augmenting responses. A comparison of these effects with those of intravenous injections of eserine and atropine will be made.

A COMPARISON OF THE EFFECTS OF INTRAVENTRICULAR γ-AMINOBUTYRIC ACID AND γ-AMINOBUTYRYL CHOLINE. P. Bach-y-Rita,* A. J. Hance,* and K. F. Killam. Depts. of Anatomy and Pharmacology, Univ. of Calif. Med. Ctr. at Los Angeles.

The effects of γ-aminobutyric acid (GABA) and γ-aminobutyryl choline (GAB-Ch) were studied on the spontaneous behavior of conscious cats with intraventricular cannulae. The GABA effects were generally depressant, while those of GAB-Ch were predominantly excitant and produced a fear-like reaction. After single intraventricular injections of 10 or 30 mg of either substance the degree and duration of the differing behavioral effects were, however, comparable. This contrasts strongly with studies on evoked cortical potentials, in which topical applications of GAB-Ch even up to 10 times the concentrations of topical GABA were ineffective (Hance, et al., this meeting). Since it has been shown that intrinsic brain levels of GABA can be lowered by thiosemicarbazide (TSC), the effects of intraventricular GABA and GAB-Ch were again compared after intraperitoneal injections of 10 mg/kg of TSC. The effects of intraventricular injections of eserine were also compared to those of GABA and GAB-Ch.

SOME ACTIONS OF MECAMYLAMINE AND NICOTINE ON THE CENTRAL NERVOUS SYSTEM. S. Ueki*, K. Koketsu*, and E. F. Domino, Dept. of Psychiatry, Univ. of Illinois, Chicago and Dept. of Pharmacology, Univ. of Michigan, Ann Arbor.

Inasmuch as the Golgi recurrent collateral on the Renshaw inhibitory neuron is a "nicotinic" type cholinergic synapse in the spinal cord, it was postulated that ganglionic blocking agents which penetrate easily into the central nervous system would act at this site. The fact that mecamylamine is a secondary amine with ganglionic blocking properties suggested that it would penetrate the blood-brain barrier and exert an action at the Golgi recurrent collateral-Renshaw cell synapse. This hypothesis was confirmed experimentally. In doses of 0.5-1.0 mg/kg given intravenously to pentobarbital anesthetized cats, mecamylamine reduced the activity of Renshaw inhibitory neurons whether activated by antidromic stimulation of the ventral root alone or after eserine and nicotine. In doses of 1.0 mg/kg given intravenously, mecamylamine raised the threshold for nicotine induced grand mal electrical seizures in unanesthetized rats paralyzed with d-tubocurarine and placed on artificial respiration.

Supported in part by the Tobacco Industry Research Committee.

EFFECTS OF MORPHINE ON SOME EVOKED ELECTRICAL RESPONSES IN THE DOG. Jane E. Heng* and E.F. Domino, Dept. of Pharmacology, Univ. of Michigan, Ann Arbor.

The actions of morphine sulfate were determined on evoked responses in the brain of unanesthetized dogs immobilized with decamethonium. Several types of evoked activity were studied including stimulation of (a) the canine tooth pulp, (b) sciatic nerve, and (c) various diffuse thalamic nuclei. In the majority of experiments the mean latency and amplitude of an evoked potential with its S.D. was determined for a series of sucessive responses before and after morphine. In 5 of 6 tooth pulp experiments in which cortical potentials could be evoked successfully in the face region of sensory area I, morphine in doses of 2 mg/kg, i.v., did not alter the latency or amplitude of the primary response. Similarly in most dogs morphine did not alter the cortical primary response following stimulation of the sciatic nerve. Subcortically, tooth evoked potentials were recorded in the reticular formation of the medulla and the midbrain and various diencephalic structures. In general following 2-10 mg/kg of morphine given i.v. there was either no effect or a definite enhancement in the amplitude of the responses. Recruiting responses recorded in the cerebral cortex following stimulation of the diffuse thalamic nuclei appeared to be enhanced by morphine in doses as low as 0.2 mg/kg, i.v.

Supported in part by Grant MY-2653, USPHS.

HYPERSYNCHRONOUS ELECTRICAL WAVES IN THE AMYGDALA OF DOGS FOLLOWING GENERAL ANESTHETICS. E.F. Domino and S. Ueki*, Dept. of Pharmacology, Univ. of Michigan, Ann Arbor.

It was reported previously (Fed. Proc. 18: 385, 1959) that during descent to and recovery from the deeper planes of anesthesia hypersynchronous waves which at times resembled an electrical seizure were observed transiently in the amygdala and related rhinencephalic structures of dogs with chronically implanted electrodes. In order to rule out the role of possible brain lesions following chronic electrode implantation as the cause of the above phenomena dogs were immobilized with decamethonium, placed on artificial respiration and prepared for acute electrical recordings. In such preparations during descent to and recovery from the deeper planes of diethyl ether anesthesia sinusoidal synchronous waves of approximately 10 to 15 cycles/sec. were observed in the amygdala and olfactory bulb. Especially in the more anterior portions of the neocortex similar activity but of much lower voltage was also observed especially with monopolar recordings. The synchronous electrical activity in the amygdala was markedly reduced in amplitude by even partial acute transection of the ipsilateral olfactory tract. It is concluded that the connections between the olfactory bulb and the amygdala and related structures are important in the development of maximal hypersynchronous waves.

Supported by grant MY-2653, USPHS, Mental Health Institute.

EMETIC ACTION OF INTRAVENTRICULAR APOMORPHINE AFTER CHRONIC ULTRASONIC MIDBRAIN TRANSECTION. H. L. Borison, W. C. Clark#* and R. Rosenstein#*. Dept. of Pharmacology, Univ. of Utah, Salt Lake City.

Cats vomit to as little as 50 mcg apomorphine HCl injected into the lateral cerebral ventricle. Ablation of the medullary emetic chemoreceptor trigger zone abolished this response (Borison, J. Physiol., in press). The concentration-volume relationship of the dose of intraventricular apomorphine required to evoke vomiting indicates that the drug reaches the emetic receptor site by displacement of cerebrospinal fluid. Use of stereotaxic ultrasound irradiation technic in more than 20 cats showed that the pathways through the midbrain could be interrupted while sparing the aqueduct. Functional transection was demonstrated acutely by hypothalamic stimulation before and after the application of ultrasound. After chronic ultrasonic transection, intraventricular apomorphine (500 mcg in 0.25 ml water) evoked emetic prodromes and vomiting within 5 min. No sign of vomiting was observed when the aqueduct was blocked. Vomiting was evoked by intraventricular apomorphine after "anemic decerebration". Retching was evoked by intracisternal apomorphine after Sherringtonian decerebration. The above evidence supports the hypothesis of a direct emetic action of intraventricular apomorphine on the medullary emetic chemoreceptor trigger zone in the cat. (Supported by USPHS Grant B-491.) #NIH Predoct. Fellows HF-9177 and HF-7870, resp.

THE EFFECTS OF ANTI-ACETYLCHOLINE AGENTS ON RHINENCEPHALIC TRANSMISSION OF EVOKED POTENTIALS. Alvin M. Revzin* and Erminio Costa. Galesburg State Research Hospital, Galesburg, Illinois.

The pyramidal cat preparation of Moruzzi was used to study the effects of atropine and some of its pharmacological analogs on the transmission of evoked potentials from the amygdala to the hippocampus. All compounds studied caused facilitation of the primary evoked potentials, enhancement of post-tetanic potentiation, and some increase of the augmenting response. JB-329 (N-ethyl-3-piperidyl cyclopentylphenyl glycolate), an experimental psychotomimetic with "atropine like" actions (Abood et al. Proc. Soc. Exp. Biol., 97: 483, 1958), caused, in addition to the above facilitations, an as yet non-quantifiable disorganization of the evoked potential patterns, of which samples will be shown. It is suggested that this disorganization of the evoked potentials may be one factor underlying the greater hallucinogenic effectiveness of JB-329 as compared to atropine or scopolamine.

THE EFFECT OF SKF6890 ON SYMPATHETIC TONE AND REFLEX DILATATION IN THE PERFUSED HINDQUARTERS OF THE DOG. A. Sakuma and L. Beck (intr. by M. H. Seevers). Dept. of Pharmacology, Univ. of Michigan, Ann Arbor.

SKF 6890A (trimethyl-[2-(2,6-xylyloxy)-propyl]-ammonium chloride, monohydrate) is capable of abolishing sympathetic tone in the perfused hindquarters of the dog. An initial decrease in the responsiveness to intra-arterial epinephrine and norepinephrine has also been observed but the loss of sympathetic tone persists longer than the decreased responsiveness to the sympathomimetic amines. By adjusting the dose of SKF 6890A it has been possible to maintain reflex dilatation in the perfused extremities when there is little or no evidence of sympathetic tone. The residual reflex dilatation can be blocked by antihistamine but not by dichloroisoproterenol or atropine.

(Supported by grant H-3946 from the USPHS)

THE EFFECT OF ELECTRICAL STIMULATION OF THE LUMBAR SYMPATHETIC ON THE PERFUSION PRESSURE IN THE HINDQUARTERS OF THE DOG. L. Beck and A. Sakuma (intr. by M. H. Seevers). Dept. of Pharmacology, Univ. of Michigan, Ann Arbor.

Electrical stimulation of the intact ipsilateral lumbar sympathetic at chosen parameters results in dilatation in the perfused hindlimb. Dilatation in the perfused area can also be obtained by stimulation of the proximal end of the divided contralateral lumbar sympathetic. Such dilatation is reduced or abolished by administration of antihistamine. Stimulation of the distal end of the divided sympathetic may produce dilatation, constriction, or biphasic responses depending on the parameters of stimulation. Administration of antihistamine decreases the dilatation or enhances the constriction dependent on the control response. Pretreatment with SKF 6890A unmasks a strong dilator component to electrical stimulation. Part of the dilatation obtained by electrical stimulation following SKF 6890A can be abolished by atropine and part by antihistamine. The significance of these observations will be discussed.

(Supported by grant H-3946 from the USPHS.)

FURTHER ELUCIDATION OF ISOPROTERENOL VASOMOTOR REVERSAL. Donald T. Wals* and Gertrude D. Maengwyn-Davies. Dept. of Pharmacology, Georgetown U. Med. School, Washington, D. C.

Isoproterenol vasomotor reversal with the aid of sympathomimetic amines has been previously reported and its peripheral nature established. l- and dl-arterenol, when used as isoproterenol reversal agents, reduced isoproterenol vasodepressor responses, but did not reverse them. This failure of arterenol to act as an isoproterenol reversal agent has been attributed to the inability of this natural neurohumor to "sensitise" the excitatory receptor site. This hypothesis was further investigated in dogs pretreated with large amounts of reserpine, in order to obtain animals depleted of endogenous arterenol. It was found that in these chronically reserpinized animals, when compared with non-reserpinized animals, a) isoproterenol reversal by phenylephrine was augmented, and b) that the dosage of phenylephrine necessary for isoproterenol reversal could be reduced by a factor of ten. Arterenol infusion in the reserpinized dog after isoproterenol reversal either reduced the height of the pressor effect or reintroduced a diphasic response. A statistical analysis of the observed phenomena was performed.

(D.T.W., Postdoctoral Research Fellow, BF-9183, and aided by Grant B-1118, National Institute of Neurological Diseases and Blindness, USPHS.)

ADRENERGIC DRUGS ON ELECTRICALLY STIMULATED ISOLATED DOG URETER. Harold H. Borgstedt (Intr. by Victor DiStefano). Dept. of Pharmacology, University of Rochester, Rochester.

The effects of some adrenergic drugs were studied on the normal isolated dog ureter in a system which provided for simultaneous recording of intraluminal pressure, perfusion rate and longitudinal contractions while electrically stimulated. Under certain controlled conditions the ureters are quiescent. In conc. in excess of 1×10^{-4}M epinephrine sometimes conditions the ureter to respond to electrical stimulation. Histamine in conc. above about 0.5×10^{-5}M has a similar effect. When, however, histamine is added in subthreshold conc. (0.1 to 0.2×10^{-5}M, previous to epinephrine, conc. of 0.1 to 0.2M are sufficient to initiate excitability exceeding that caused by either drug alone. Diphenhydramine (about 0.4×10^{-5}M) prevents this sensitizing effect of histamine when added before completely, if added after the other drugs, when excitability is established, only incompletely. Isoproterenol and Lilly 20522 (Dichloroisopropylnorepinephrine) inhibit and abolish electrical excitability in certain concentrations.

EFFECT OF NOREPINEPHRINE ON THE RESPONSE TO SYMPATHETIC STIMULATION. J.H.Burn and M.J.Rand.* Department of Pharmacology, University of Oxford, Oxford, England.

The vasoconstriction in the dog's hindleg produced by stimulation of the lumbar sympathetic trunk in the presence of atropine is enhanced by a previous infusion of norepinephrine. At the same time the threshold strength of stimulation to produce vasoconstriction is reduced. These effects have been observed in the normal dog and also in the reserpine-treated dog. The vasodilatation produced by sympathetic stimulation in the muscles of the dog's leg, which is an effect produced by sympathetic cholinergic fibres, is altered by an infusion of norepinephrine to a response which shows an after-phase of vasoconstriction. It is suggested that the response to sympathetic stimulation is determined by the amount of norepinephrine in the neighbourhood of the sympathetic nerve endings. The presence of extractable norepinephrine in arteries and veins was demonstrated by Schmiterlöw in 1948. This appears to be a store which can be filled from norepinephrine in the blood. The function of the norepinephrine secreted by the adrenal medulla may be to keep the store full.

MODE OF ACTION OF THE SYMPATHOMIMETIC ALDEHYDES. N. R. Eade (intr. by K. I. Melville), Department of Pharmacology, McGill University.

Simple aldehydes such as acetaldehyde, propionaldehyde and butyraldehyde have pronounced sympathomimetic activity, a surprising property in view of their structure. The effects of injection of these aldehydes include a rise in blood pressure, contraction of the nictitating membrane and pupillary dilatation; these responses can be potentiated by cocaine and ephedrine and antagonized by sympatholytics. The blood pressure and the contractions of the nictitating membrane were recorded in experiments on spinal cats in which both adrenal veins had been ligated. In reserpinized animals depleted of their catechol amines, it was not possible to elicit any sympathomimetic response to injected aldehydes. It appears that the sympathomimetic activity of these compounds is due to the liberation of catechol amines from tissue depots. These simple aldehydes have proved to be useful tools for the study of amine release from such sites. (Aid by a Grant from the National Research Council of Canada).

BLOOD PRESSURE AND ECG RESPONSES TO EPINEPHRINE AND NOREPINEPHRINE IN UNANESTHETIZED NORMAL AND HYPERTHYROID RABBITS. R. Martel* and K. I. Melville, Dept. of Pharmacology, McGill University, Montreal, Canada.

Blood pressure was recorded with a Sanborn transducer from a polyethylene tube inserted under local procaine (2%) through the femoral artery into the abdominal aorta of "normal" rabbits: and the procedure repeated on the same animals rendered "hyperthyroid" by injections of sodium liothyronine (100 to 200 mg. S.C. for 3 to 5 days). Simultaneous ECG (Lead II) changes were also recorded, and injections made into a marginal ear vein from a needle connected with a fine polyethylene tubing attached to a syringe. Effects of equal doses of epinephrine and norepinephrine, ranging from 1.6 to 16 mg./kg. were compared. It was observed that both the cardiac (bradycardia, tachycardia and ectopic rhythms) and the vascular (pressor) responses to the catecholamines are potentiated in the hyperthyroid state. Under both conditions, ventricular fibrillation occurred rarely (1 instance in each) and ectopic rhythms were abolished by atropine or hexamethonium. It is concluded that in the hyperthyroid state there is increased cardiovascular sensitivity to injected catecholamines. The findings also suggest that ventricular arrhythmias in hyperthyroidism are not due to any direct effect of the thyroid hormone. The problem is being further studied. (Supported by a Quebec Health Grant).

ADRENERGIC AGENTS AND RESERPINE. Virginia L. Sydow and Raymond P. Ahlquist. Dept. of Pharmacology, Medical College of Georgia, Augusta, Ga.

The pressor responses of the anesthetized mongrel dog to levarterenol and l-epinephrine are markedly potentiated by the prior administration of reserpine. It has been hypothesized that this potentiation occurs consequent to a depletion of catechol amines after a period of several days treatment with reserpine; however, we find that the potentiation appears within 15 minutes after the administration of reserpine. It was noted that this potentiation occurred only in regard to epinephrine and arterenol and very closely related compounds (e.g. methyl-epinephrine, methyl-arterenol) and not with ephedrine, paredrine, methylphenidate, Hecylamine, etc. It is possible that reserpine and/or similar agents may provide a method for distinguishing between true sympathomimetic agents and pseudo-sympathomimetics. It has also been observed that after chronic administration of reserpine, the test drugs, ephedrine etc., are relatively ineffective as pressor agents, but, that if epinephrine or levarterenol is given immediately before the test drug, the drug displays its usual pressor activity. This observation might lead one to suppose that epinephrine or arterenol is necessary for a normally functioning receptor. It has also been observed that administration of a ganglionic blocking agent before reserpine, but not after, preserves the usual response to ephedrine and the other tested drugs.

INFLUENCE OF RESERPINE ON ADRENAL MEDULLARY RESPONSES TO DIRECT CHEMICAL STIMULATION. E.F. Woods, J.A. Richardson and E.E. Bagwell*. Dept. of Pharmacology, Med. College of S. C., Chas.

Determinations of changes in plasma catechol amines produced by injection of minute quantities of nicotine into the thoracic aorta provide an excellent means of evaluating adrenal medullary responsiveness. In this study, the effects of reserpine on the adrenal responsiveness to nicotine (10-20 γ/kgm were determined and correlated with changes in cardiovascular function. Experiments were carried out in 32 vagotomized open-chest dogs under barbiturate anesthesia. Plasma catechols, heart contractile force and arterial pressures were determined by methods previously described (J. Lab. & Clin. Med. 47: 832, 1956; P.S.E.B.M. 84: 263, 1953). Reserpine was administered intramuscularly in doses varying from 0.05 to 1.00 mgm/kgm daily for periods ranging from 1 to 7 days. Reserpine did not significantly alter the contractile force and blood pressure responses produced by adrenal stimulation with nicotine. However, the increments in plasma epinephrine levels coincident with the cardiovascular changes were significantly less in reserpinized animals than in control preparations. The mean plasma epinephrine level produced by 10 γ/kgm of nicotine was 4.7 γ/liter after reserpine, as compared to 15.6 γ/liter in the controls. Reserpine also markedly reduced the cardiac effects of sympathetic nerve stimulation. (Aided by U.S.P.H.S. Grants H-1846 and HTS-5200)

COMPARISON OF RACEMIC CARBINOXAMINE WITH ITS OPTICALLY ACTIVE ISOMERS. Adolph P. Roszkowski* and William M. Govier. Dept. of Pharmacology, McNeil Laboratories, Inc., Philadelphia, Pa.

Resolution of carbinoxamine [(±)-CBX] (I) into two optically active isomers has prompted us to investigate the antihistaminic and general pharmacological activity of these isomers. Using the isolated guinea pig ileum, it was shown that (+)[(-)-CBX tartrate] (II), was the most active agent in inhibiting supramaximal histamine induced contractions, the ED_{50} being 0.26 μg/100 ml. The ED_{50} of I was 1.9 times as great as that of II. (-)[(+)-CBX maleate] (III) was 29 times less active than II. For an estimate of in vivo potency, male guinea pigs were treated i.p. with varying doses of I and its isomers and challenged 20 min. later with a lethal i.v. injection of histamine (3 mg/kg). The ED_{50} for II was 50 μg/kg and for I 90 μg/kg. III was approximately 34 times less active than II. II caused at least a 50% blockade of the depressor response to an i.v. injection of 2-4 μg/kg histamine with doses of 42-46 μg/kg i.v. in the anesthetized dog. Doses of 13-106 μg/kg of I and 11 mg/kg of III were required to produce such a blockade. I and its isomers also possessed mild anticholinergic properties in vitro and the order of anticholinergic activity appeared to parallel their antihistaminic activity. Toxicity studies revealed that the action of these drugs was not isomer dependent with respect to induction of convulsions or lethality.

PHARMACOLOGY OF A NEW, POTENT, ORALLY ACTIVE ANTIHISTAMINIC DRUG, SU-6518. W. E. Barrett, C. F. Huebner*, A. J. Plummer and A. Deitrich*. Research Dept., CIBA Pharmaceutical Products Inc., Summit, N. J.

Su-6518 has been studied on the isolated ileum of the guinea pig for its antihistaminic activity. At a concentration of 0.005 γ/ml, Su-6518 produced a 50 per cent inhibition of the contraction of the ileum evoked by histamine. The drug was administered orally to guinea pigs by intubation 1, 3 and 6 hours prior to challenging the guinea pigs with a fatal dose of histamine. The dose (ED_{50}) that protected 50 per cent of the guinea pigs was calculated for each of the three time intervals. The ED_{50} values obtained were: 1 hour - 66.4 γ/kg ± 11 γ (SE); 3 hours - 243 γ/kg ± 37 γ (SE) and 6 hours - 3.0 mg/kg ± 0.33 mg (SE). Su-6518 was found to be more active than either Pyribenzamine(R) or Chlortrimeton as an antihistaminic drug. Su-6518 at a dose of 150 γ/kg protected one-half of the sensitized guinea pigs from fatal anaphylactic shock when these pigs were challenged with the antigen (horse serum). Some of the general pharmacological properties of Su-6518 will be presented.

EVALUATION OF HYDROCORTISONE-INDUCED ENZYME SYNTHESIS IN THE ADRENALECTOMIZED RAT. Donald C. Kvam* and R. E. Parks, Jr., Dept. of Pharmacology and Toxicology, Univ. of Wis., Madison.

Several laboratories have reported hepatic glucose-6-phosphatase and fructose-1,6-diphosphatase activities to be increased after glucocorticoid administration and in diabetes. This study shows that these increased activities brought about by hydrocortisone injection can be blocked by the administration of the amino acid antagonist, ethionine. This inhibition can be prevented by the simultaneous injection of methionine. For six hours after initial hydrocortisone injection (with and without ethionine) comparable increases in blood sugar and hepatic glycogen levels occur without significant change in either phosphatase activity. However after forty-eight hours it was found that when enzyme synthesis is inhibited by ethionine, glycogen and blood sugar levels rise, but to levels significantly below those of animals receiving hydrocortisone alone. These findings suggest that the increases in these enzymatic activities play no role in the primary mechanism of steroid-induced gluconeogenesis, but that they represent true enzymatic adaptations, produced by these hormones, which allow a more complete adjustment of the metabolic machinery.

INHIBITION OF ANAPHYLACTOID EDEMA IN THE RAT BY 2-DEOXYGLUCOSE. Andres Goth, Dept. of Pharmacology, U. of Texas Southwestern Med. School, Dallas, Tex.

Previous studies have shown that the anaphylactoid reaction of rats to dextran or ovomucoid could be inhibited by alloxan diabetes, the inhibition being reversible by pretreatment with insulin. The present work shows that the glucose analogue 2-deoxyglucose is capable of inhibiting this type of inflammatory reaction.

A dose of 200 mg/kg of 2-deoxyglucose was sufficient to prevent the effect of 60 mg/kg of dextran or 10 mg/kg of ovomucoid when these compounds were injected by the intravenous route. The inhibitor exerted its effect in less than 15 minutes.

The reaction of rats to compound 48/80 was not inhibited, indicating a different mechanism of action for this histamine releaser.

Insulin pretreatment opposed the action of 2-deoxyglucose competitively. These results suggest an important role of carbohydrate metabolism in certain types of inflammation associated with histamine release.

THE TEMPERATURE DEPENDENCE OF THE LOCALIZED SHWARTZMAN PHENOMENON. W.R. Burack and W.F. Mosimann (intr. by Paul Hagen). Dept. of Pharmacology, Harvard Med. School, Boston, Mass.

The Shwartzman reaction usually fails to appear on the abdominal skin of rabbits tied in the supine position. This restraint is associated with a fall in abdominal skin (and rectal) temperature. If in a restrained rabbit the site of the preparatory intradermal endotoxin injection is warmed (38-40°C) at the time that the provocative intravenous endotoxin is given, the reaction will develop. The Shwartzman phenomenon can be elicited in mice kept at room temperature (25°C) but is greatly inhibited if the mice are kept in the refrigerator (5°C). It appears that the development of the localized Shwartzman phenomenon depends upon local tissue temperature. (Supported by USPHS Grants HF-6523, B-1470 and 2-G-95.)

CELLULAR PROLIFERATION OF INTESTINAL EPITHELIA IN THE RAT 2 MONTHS AFTER PARTIAL RESECTION OF THE ILEUM. M. R. Loran and T. L. Althausen (intr. by R. M. Featherstone). Dept. of Medicine, University of California School Med., San Francisco, Calif.

Sprague-Dawley rats subjected to a 10% resection of the lower ileum and their controls were injected with tritiated thymidine and sacrificed at 2 and 23 hours. Segments of the duodenum, jejunum and ileum were radioautographed, and the migration of the cells at 23 minus 2 hours was measured with an eyepiece micrometer. In the control animals, the cells migrated 35, 42 and 34% of the total distance from the crypts to the tips of the villae in the duodenum, jejunum and ileum, respectively, and in the resected animals 43, 90 and 82% of the total distance. These data demonstrate that the rate of cell renewal is considerably greater in the resected intestine than in the normal intestine. These results will be discussed in relationship to hypertrophy and metabolic changes in the small intestine following resection. The therapeutic implications of these studies will also be discussed.

KININS PRODUCED FROM COLOSTRUM BY KALLIKREIN OR SALIVA. Paul S. Guth (Intr. by M. A. Spirtes). Inst. of Animal Physiology, Cambridge, England, and Dept. of Pharmacology, Hahnemann Medical College, Phila., Pa.

Substances capable of stimulating smooth muscle are produced on the incubation of bovine colostrum with urinary kallikrein or calf saliva. These kinins will be differentiated from kallidin, substance A and similar smooth muscle activating agents. The kinin produced when saliva and colostrum are incubated is likely to be formed in the suckling calf. Further as colostrum becomes milk, the ability to form these kinins diminishes. These data have stimulated speculation on the role of these kinins in the physiology of the new-born. (P.S. Guth is a fellow of the National Paraplegia Foundation).

DISTRIBUTION AND EXCRETION OF HEPARIN-S^{35}. T. A. Loomis, Dept. of Pharmacology, University of Washington, Seattle, Washington

Heparin-S^{35} was extracted from the liver of dogs injected with $Na_2S^{35}O_4$. The product was free of inorganic sulfate, had an activity of 48,000 c/m/mgm, and assayed 64 U. S., P. anticoagulant units/mgm. Rats injected with Heparin-S^{35} (5 mgm/kg i. v.) were sacrificed at 2, 6, 12, 18, and 24 hours. Analyses were performed in digests of blood, kidney, liver, spleen, lung, heart, intestine, skeletal muscle, skin and mast cells. Initially, activity was high in plasma or serum and low in blood cells or clot. Activity diminished in the blood in 6 to 12 hours, but persisted in the liver and spleen for 18 to 24 hours. Mast cell radioautography indicated the presence of radioactivity in the granules. Three dogs were administered Heparin-S^{35} (0.5 mgm/kg). Blood and urine biological and radioactivity assays were performed on samples obtained at 15 minute intervals. Urinary excretion rate of Heparin-S^{35} varied directly with blood concentration. 20 to 30% of injected Heparin-S^{35} was recovered in the urine in 90 minutes when anticoagulant activity of the blood had returned to normal.

INTESTINAL ABSORPTION OF A HEPARIN-METHYL ESTER. B. Salafsky* (Introduced by T. A. Loomis) Department of Pharmacology, University of Washington, Seattle.

Sodium Heparin was placed in a 0.035 N methanolic HCl solution for 1 hour at room temperature. The suspension was then taken to dryness in-vacuo. The extent of esterification and desulfation of the product was determined by infra-red absorption, acid-base titrations, electrophoretic pattern, mass spectrographic analysis, sulfur and methoxy determinations, and C^{14} methanol preparations. Two-hundred mgm of the ester, dissolved in buffer solutions having as the final pH was 4.0 or 5.0, was placed in a washed ligated segment of a dog's duodenum the blood supply of which was left intact. A significant systemic anticoagulant effect occured after ½ to 1 hour and lasted 2 to 3 hours. Upon examination of the segment no local tissue irritation was noted.

TOXIC EFFECT OF A MATERIAL ISOLATED FROM HYDRA LITTORALIS. Edward S. Kline* and Vaman S. Waravdekar. Biochemistry Branch, Armed Forces Institute of Pathology, Washington, D. C.

We have previously reported (Fed. Proc. 18: 512, 1959) that a material isolated from homogenates of Hydra littoralis possesses a property to inhibit succinoxidase activity. We feel that this material is a component of the toxin present in the nematocysts (stinging bodies) of these animals. The material has been purified, and the experimental evidence indicates that it is a protein or possibly a protein complex. It has been established by many investigators that homogenates of, or crude extracts of nematocysts from, coelentrates are toxic to experimental animals. We have found that the purified material isolated from Hydra homogenates is toxic to such animals. The data on the toxicity of this material will be presented.

EFFECTS OF EPINEPHRINE COMBINED WITH ACETYLCHOLINE OR WITH EPINEPHRINE ANTAGONISTS ON CARDIAC RATE, AMPLITUDE, AND GLYCOGEN. Norma H. Vincent* and Sydney Ellis. Dept. of Pharmacology, Woman's Medical College of Penna., Philadelphia, Pennsylvania.

Langendorff preparations of male guinea pig hearts were perfused with Krebs-bicarbonate solution at 27°C. Epinephrine, 3.3 mcg/min., infused for one hour produced an average increase of 44% in cardiac rate and of 38% in amplitude of beat and a decrease in atrial glycogen to 35% and of ventricular glycogen to 25% of the glycogen content of control hearts. The dichloro analog of isoproterenol (DCI), 4 mcg/min., prevented the increase of amplitude and rate and reduction of glycogen by epinephrine. In the presence of veratramine, 1 mcg/ml, which maintained rate at control levels, epinephrine, 3.3 mcg/min., increased amplitude and decreased glycogen levels 50%. Acetylcholine, 18 mcg/min., infused with epinephrine, 3.3 mcg/min., resulted in glycogen levels equivalent to those of control hearts with a decrease of 55% in rate and of 18% in amplitude. At 37.5°C infusion of epinephrine and acetylcholine plus epinephrine produced effects on rate, amplitude, and glycogen similar to those obtained at 27°C. It would appear that acetylcholine can antagonize the glycogenolytic effect of epinephrine as well as the effect of epinephrine on rate and amplitude. (Supported in part by U.S.P.H.S. Grant B-1657).

DETERMINATION OF PHOSPHORYLASE IN FROZEN AND NON-FROZEN RAT HEART. Niels Haugaard, Marilyn E. Hess*, Walther R. Kukovetz* and Joseph Shanfeld*. Laboratory of Pharmacology, University of Pennsylvania, School of Medicine, Philadelphia, Pa.

The activity of phosphorylase a in heart muscle has usually been found to be quite high (see Hess, M.E. and Haugaard, N., J. Pharmacol., 122, 169, 1958). Recent experiments from this laboratory indicate that the true value may be considerably lower. Extracts were made of perfused hearts from normal rats by two methods: 1) by grinding the heart with sand in cold NaF-EDTA solution and 2) by freezing the heart in alcohol-CO_2 mixture followed by procedure 1. It was found that the ratios of phosphorylase a to b in extracts prepared by method 2 were invariably higher than in extracts prepared by procedure 1. In addition after treatment with an anion exchange resin (Dowex-1 in the chloride form) the phosphorylase ratios had the same low value in extracts prepared by either method. UV-absorption and paper chromatography showed that the resin effectively removed nucleotides such as AMP. Analyses of inorganic and easily hydrolyzable phosphate showed that freezing was associated with extensive breakdown of ATP. It appears that breakdown products of ATP (probably mainly AMP) cause activation of phosphorylase b. If precautions (such as high dilution or removal of nucleotides) are taken the phosphorylase ratios in control perfused hearts range from 10 to 20%. In extracts from hearts stimulated by sympathomimetic drugs the ratio is increased progressively with dose to a maximum of 50 to 60%.

PHOSPHORYLASE ACTIVITY IN HEART MUSCLE. Julius Belford and Marcia R. Feinlieb*. Dept. of Pharmacology, State Univ. of N.Y. Downstate Medical Center, Brooklyn, N.Y.

In the isolated guinea pig auricle calcium and strophanthin-K increased the per cent phosphorylase a concomitant with their positive inotropic actions. However concentrations of these agents which depressed force of contraction also gave rise to increased levels of phosphorylase a. A three hour period of 1 per second stimulation which produced no overt contractile depression in the isolated guinea pig auricle, lowered the per cent phosphorylase a. Epinephrine increases force of contraction as well as the per cent of phosphorylase a in the isolated rat auricle. Depression of the isolated rat auricle with anoxia, quinidine or pentobarbital did not result in any significant change in phosphorylase a. 'Failure' induced by prolonged high frequency stimulation of the isolated rat auricle resulted in significant lowering in per cent phosphorylase a. 'Failure' induced in the intact cat by similar stimulation also produced a significant decline in per cent ventricular phosphorylase a. Hemorrhagic hypotension in the intact cat did not alter phosphorylase a content. In the intact cat, digitoxin did not significantly affect phosphorylase a activity at arrythmia inducing dose levels. Supported by grant from the N.I.H. (H-3724).

DISTRIBUTION OF MUSCLE PROTEINS IN THE NODE AND FIBERS OF THE CONDUCTION BUNDLE OF THE BEEF HEART. E. W. Emmart (NIAMD), NIH, Bethesda, Maryland and E. Helander*(University of Gothenburg) Sweden.

By means of fluorescent rabbit antisera to beef heart muscle proteins, a study has been made of the cytological localization of these proteins in the node and fibers of the conduction bundle of the beef heart. Antisera to muscle proteins isolated from heart muscle show a high degree of specificity for myofibrils. Antisera to components of the myosin molecule are capable of cross reaction.

ENZYMATIC INACTIVATION OF ADENOSINE-3',5'-PHOSPHATE BY PREPARATIONS FROM HEART. R. W. Butcher, Jr.* and Earl W. Sutherland. Dept. of Pharmacology, School of Med., Western Reserve Univ., Cleveland, O.

Adenosine-3',5'-phosphate (cyclic 3,5-AMP) has been shown to be involved in the action of several hormones, in various tissues, via the enhancement of tissue levels of active phosphorylase. Cyclic 3,5-AMP accumulated in increased amounts when catechol amines were added to particulate preparations from heart, the isopropyl derivative being the most active. Caffeine increased the accumulation of cyclic 3,5-AMP in the presence of the catechol amines. The presence of a cyclic 3,5-AMP inactivating mechanism has been reported previously. The product was adenosine-5-phosphate, and hence the enzyme was designated a phosphodiesterase. The cyclic 3,5-AMP phosphodiesterase recently has been purified extensively from beef cardiac ventricle. Its action was accelerated by imidazole. It was inhibited by low levels of methyl xanthines, with theophylline being considerably more effective than caffeine or theobromine. It seems possible that the cardiac inotropic effects of the methyl xanthines may be due to the inhibition of the cyclic 3,5-AMP phosphodiesterase.

EFFECT OF ACETYL STROPHANTHIDIN ON ALDOSTERONE SECRETION IN THE INTACT ANESTHETIZED DOG. Allen W. Gemoll* and Theodore R. Sherrod. Dept. of Pharmacology, Univ. of Ill. Coll. of Med., Chicago, Ill.

Previous work in this laboratory on the renal hemodynamic and electrolyte effects of acetyl strophanthidin showed that this drug produced an increased urinary excretion of Cl, Na and K. At the same time plasma Cl and Na were also elevated, while plasma K tended to increase, but this change was quite variable. The present investigation was done to determine the action of acetyl strophanthidin on the secretion of aldosterone by the adrenal cortex in an attempt to correlate the electrolyte alterations incident to the administration of this digitalis-like drug. Using mongrel dogs under ether anesthesia the right lumbo-adrenal vein was cannulated and adrenal venous blood samples were collected prior and subsequent to administration of acetyl strophanthidin. The cortical steroids were extracted from the blood samples and the aldosterone fraction of the blood steroids was isolated by paper chromatography using the Zaffaroni Ethylene Glycol Toluene, the Eberlein-Bongiovanni E_2B and the Bush B_5 systems respectively. Aldosterone was quantitated by the blue tetrazolium reaction. Following the administration of 1.2 mgm, total dose, of acetyl strophanthidin the venous blood flow from the right adrenal gland diminished. Plasma Cl, Na and K increased above control levels while the secretion of aldosterone decreased. (These studies aided by Grant # H2354C2 from the Dept. of Health, Education and Welfare, USPHS.)

THE EFFECT OF DIGOXIN ON THE INTERMEDIARY METABOLISM OF THE INTACT DOG HEART AS MEASURED WITH GLUCOSE-C^{14}. Gerald A. Kien* and Theodore R. Sherrod. Dept. of Pharmacology, Univ. of Ill. Coll. of Medicine, Chicago, Illinois.

These experiments were specifically designed to correlate the cardiac hemodynamic action of a therapeutic dose level (0.065 mgm./kgm. body weight) of digoxin with possible alterations in the dynamics of the intermediary metabolic pathways involved in the myocardial utilization of glucose-C^{14} in the normal dog. Administration of this dose of digoxin resulted in an augmentation of the glucose utilization of the myocardium accompanied by a greatly increased rate of glycolysis and oxidative activity of the heart. The contribution of glucose to the total metabolism of the myocardium was increased and the utilization of non-carbohydrate substrates was decreased. These metabolic changes occurred in the absence of changes in the dynamic functions of the heart, indicating that the metabolic alterations were due to a primary effect of the drug rather than an effect secondary to an altered state of cardiac activity. (These studies were aided by Grant # H2354C2 from the Department of Health, Education and Welfare, United States Public Health Service.)

EFFECT OF CARDIAC GLYCOSIDES ON PLASMA VOLUME IN THE DOG. Marion deV. Cotten. Dept. of Pharmacology, Emory Univ. School of Medicine, Atlanta, Georgia.

The effects of cardiac glycosides on the T-1824 (plasma volume) and thiocyanate (extracellular water) spaces, hematocrit, hemoglobin and plasma proteins have been studied in both anesthetized and conscious dogs. After intravenous injection of T-1824 and thiocyanate, arterial blood samples were obtained at 60, 90 and 120 minutes. At this time either a glycoside or its solvent was injected; blood samples were then obtained at 10, 20, 30, 45, 60, 120, 180 and 240 minutes after injection of the glycoside or its vehicle. In 19 anesthetized dogs ouabain (0.05 mg/kg) and digitoxin (0.13 mg/kg) increased slightly the plasma volume, hematocrit and hemoglobin, but had no effect on the thiocyanate space or plasma proteins. Nine conscious dogs given 0.05 mg/kg ouabain showed a slight decrease in plasma volume, but no changes in other values. Five conscious and 7 anesthetized dogs given the glycoside solvent instead of a glycoside showed no changes in any of the measured parameters. It is concluded that the decrease in venous return and cardiac output seen in normal dogs after digitalization is not due to a decrease in circulating blood volume.

CARDIAC ACTION OF SATURATED FATTY ACIDS. George E. Price* and Reinhard H. Reutner. College of Osteopathic Medicine & Surgery, Des Moines, Iowa.

Young male white rats were fed on a diet containing 55% of saturated fat or fatty acids. They died after a week or 10 days. Addition of 2% or more of unsaturated fatty acid prevented the effect. These experiments will be continued under various conditions, in order to test the theory, that nutrition plays a major role in the etiology of various forms of cardiac disease. These experiments seem to support the hypothesis that oxidation of unsaturated fat may furnish the energy for cardiac contractions. Experiments, furnishing additional evidence, will be described later. Evidence is available to show that all electromotive forces in tissues are composed of potential differences, located at the phase boundary of several immiscible conductors.

Supported by Research Grants from the National Heart. Inst. P.H.S. Bethesda, Md. and the American Heart Assoc., New York.

EVALUATION OF INOTROPIC EFFECTS OF DRUGS ON THE EMBRYONIC HEART BY MEANS OF A NEW TECHNIC. Leslie P. McCarty*, Woo Choo Lee*, and Frederick E. Shideman. Department of Pharmacology and Cardiopulmonary Research Laboratory, Univ. of Wisconsin, Madison.

A photoelectric method of recording contractile amplitude, tone and rate of the embryonic chick heart has been devised and will be described. The hearts from embryos 3 or 4 days old or older have been employed. Embryonic hearts respond to epinephrine in concentrations as low as 10^{-10} whether extrinsically innervated or noninnervated. 1-(3,4-Dichlorophenyl)-2-isopropylaminoethanol (dichloroisoproterenol) is capable of blocking the effects of epinephrine or norepinephrine but not barium or ouabain on the heart either prior to or after it receives its extrinsic nerve supply. Acetylcholine is active on all hearts in a concentration as low as 10^{-8}. Physostigmine potentiates the effects of acetylcholine on hearts from 4 day-old or older embryos but does not alter the effects of acetylcholine on the heart from the 3 day-old embryo. The sensitivity of the embryonic myocardium to epinephrine and acetylcholine does not increase with innervation which indicates the function of the receptor sites for these drugs is fully developed prior to extrinsic innervation.

DRUG METABOLISM

Chairman: T. C. Butler Room N-204, Memorial Building

ADAPTIVE INCREASES IN DRUG METABOLIZING ENZYMES INDUCED BY PHENOBARBITAL AND OTHER FOREIGN COMPOUNDS. A. H. Conney*, C. Davison, C. Glasgov* and J. J. Burns. National Heart Inst., Bethesda, Md. and Goldwater Memorial Hospital, N.Y.

Administration of phenobarbital, barbital, 3-methylcholanthrene or 3,4-benzpyrene to rats induces marked increases in the activities of several drug metabolizing enzymes in liver microsomes. Examples of enzymes which are increased include azo dye N-demethylase, 3,4-benzpyrene hydroxylase and zoxazolamine hydroxylase. This stimulatory effect is also exerted by thiopental, Chloretone, phenylbutazone, aminopyrine and orphenadrine as measured by their ability to increase the activity of azo dye N-demethylase. These in vitro data are in accord with in vivo observations; the duration of action of a paralytic dose of zoxazolamine is considerably shortened in rats pretreated with phenobarbital, 3,4-benzpyrene or with 3-methylcholanthrene. Furthermore, a drug can enhance the activity of enzymes required for its own metabolism. For instance, pretreatment of weanling rats with phenylbutazone for 4 days causes a large increase in the activity of the hepatic enzyme system which metabolizes phenylbutazone. Similarly, pretreatment of rats with aminopyrine increases the activity of the liver enzyme system which N-demethylates aminopyrine. These increases in drug metabolizing enzymes represent a new type of adaptive response to drugs.

INHIBITION OF HEXOBARBITAL METABOLISM BY CHLOROTHION (p-NITRO-m-CHLORO PHENYL DIMETHYL THIONOPHOSPHATE). R. M. Welch*, P. Rosenberg* and J. M. Coon. Dept. of Pharmacology, Jefferson Med. College, Philadelphia, Pa.

The anticholinesterase Chlorothion and several other insecticidal organic phosphate compounds which are rapidly metabolized by the liver have been shown to prolong hexobarbital sleeping time in mice. In-vitro studies indicate that liver slices taken from mice which received Chlorothion orally 2 hours before or liver slices to which Chlorothion was added directly detoxified hexobarbital slower than did controls. Liver slices treated with 10^{-4}M Chlorothion metabolized 52% of added hexobarbital while controls metabolized 75% over the same period. In-vivo studies consisted in determining brain and plasma levels of hexobarbital at various times after intravenous injection of hexobarbital. From one minute after injection to the time of recovery from anesthesia brain and plasma levels of hexobarbital were consistently higher in mice receiving Chlorothion orally 2 hours previously. All mice receiving hexobarbital, whether treated with Chlorothion or not, recovered when 25±2 mcg/gm of hexobarbital was reached in the brain. This indicates that sensitization of the site of action of the barbiturate by Chlorothion could not account for prolongation in sleeping time. The organic phosphates which prolong hexobarbital sleeping time may interfere in some way with the microsomal mechanism for oxidizing this barbiturate.

PHYSIOLOGICAL DISPOSITION AND URICOSURIC EFFECT OF A KETO ANALOGUE OF OXYPHENBUTAZONE. Peter G. Dayton*, J. E. Seegmiller* and J. J. Burns. National Heart Institute, National Institute of Arthritis and Metabolic Diseases, Bethesda, Md. and N.Y.U. Research Service, Goldwater Memorial Hospital, New York.

Phenylbutazone is converted in man to a metabolite having an hydroxyl group in the para position of a benzene ring (Metabolite I, oxyphenbutazone). Oxyphenbutazone has potent antirheumatic effect but little uricosuric activity in gouty subjects. However, introduction of a keto group on the alpha carbon of the butyl side chain yields a compound (G-29701) which has potent uricosuric effect but little antirheumatic activity. This simple structural change markedly increases acidity of the molecule; oxyphenbutazone has a pK_a of 4.6 whereas its keto derivative has a pK_a of 2.3. The potent uricosuric activity of G-29701 was predicted from previous observations which showed that structural changes which increase acidity in the phenylbutazone series enhance uricosuric activity (Nature, 182, 1162 (1958)). The lack of antirheumatic activity observed with G-29701 can be explained by its more rapid disappearance in man (half life 4 hours) compared to oxyphenbutazone (half life 72 hours).

INHIBITION OF HEXOBARBITAL METABOLISM BY JB-516 (BETA-PHENYLISOPROPYLHYDRAZINE). K. B. Pearce, J. M. Fujimoto and G. L. Plaa (intr. by F. W. Schueler). Dept. of Pharmacology, Tulane Med. School, New Orleans, La.

JB-516 prolonged sleeping time. Mice pretreated 30 minutes with JB-516 (20 mg./kg., s.c.) had hexobarbital (100 mg./kg. i.p.) sleeping times of 93 ±8.6 minutes compared to 42.7 ±6.4 minutes for controls ($p=.001$). For pentobarbital (75 mg./kg., i.p.), the sleeping times were 91 ±7.2 and 39.4 ±8.9 minutes respectively ($p=.001$). Prolongations of sleeping times were correlated with higher barbiturate levels. Control hexobarbital (200 mg./kg., i.p.) total body levels in mice were 29.3 ±4.8 mg./kg. at one hour; JB-516 (20 mg./kg.) treatment gave 81 ±3.5 mg./kg. ($p=.001$). With pentobarbital (75 mg./kg., i.p.) respective recoveries were 16.8 ±1.4 and 4.5 ± 7.1 mg./kg. Further support for the hypothesis that JB-516 inhibits barbiturate biotransformation was obtained in the isolated rat liver perfusion system. Disappearance of hexobarbital from the perfusate was inhibited by JB-516. Recoveries of hexobarbital (50 mg. added) in the perfusates at 120 minutes were 2.8% versus 84% and 22% versus 100% in paired experiments of controls versus JB-516 (20 mg., 15 minutes before hexobarbital addition) respectively. The levels in the livers were practically identical.

Supported by grant RG-5514 from US Public Health Service)

THE METABOLISM OF MESCALINE-C^{14} BY THE DOG. Elliot Spector (Introduced by C. J. Kensler), Dept. of Pharmacology and Experimental Therapeutics, Boston Univ. School of Medicine, Boston, Mass.

Mescaline (3,4,5-trimethoxyphenyl[α-C^{14}]ethylamine) was administered to anesthetized female dogs in a dose of 5 or 20 mg/kg (representing 10 to 15 μc). Sixty per cent or more of the administered radioactivity was excreted in the urine within 8 hours. The urine, acidified and subjected to ion exchange chromatography on Dowex-1 formate, revealed the presence of two peaks of radioactivity. The first peak was identified as unchanged drug. The metabolite, representing approximately 60% of the total urinary radioactivity was obtained in crystalline form and gave a sharp melting point at 96° C (uncorrected). Infrared analysis indicated the presence of an indole ring with a hindered hydroxyl, a tertiary nitrogen and no carbonyl or carboxyl group. Elemental analysis gave an empirical formula of $C_8H_9O_3N$. Evidence that chemical alteration of mescaline was not the result of bacterial action in the urine and/or processing procedures was provided by appropriate control experiments.

SOME IMPORTANT ASPECTS OF THE PHARMACOLOGY OF METHDILAZINE. John H. Weikel, Jr. and Paul M. Lish*. Dept. of Pharmacology, Mead Johnson and Co., Evansville, Indiana.

Methdilazine [10-(1-methyl-3-pyrrolidylmethyl) phenothiazine], synthesized by Feldkamp and Wu, had consistently greater activity in four different species than some of the most potent available antihistamine agents. It was outstanding in its ability to inhibit the increased capillary permeability induced by several methods, and in its ability to protect cats and mice from shock produced by the endotoxin from E. coli, and rats from the effects of pulmonary edema caused by intraperitoneal injection of ammonium chloride. Methdilazine was rapidly absorbed from the gastrointestinal tract, and very rapidly cleared from the blood stream. Although the duration of action was quite long there was complete clearance of the important tissues within 48 hours of either a single dose or the last of four daily doses of 12 mg/Kg. There was a lesser degree of concentration in the brain than reported for other phenothiazine derivatives. This was reflected in a wide margin between dosages giving antihistaminic effects and those affecting the central nervous system. Methdilazine had a lower acute toxicity than other agents of less potency, and caused no functional or pathological changes in chronic toxicity studies of one year.

TRYPTOPHAN AND KYNURENINE INHIBITION OF IN VITRO THYROXINE EFFECTS. R.H.Lindsay*, R.W.Hanson* and S.B.Barker. Dept. of Pharmacology, Univ. of Ala. Med. Center, Birmingham 3, Ala.

In vitro thyroxine maintenance of rat kidney slice oxygen consumption in a Ringer-proline medium was accompanied by a greater net production of glucose, ammonia nitrogen and glutamic acid than in controls. The addition of tryptophan and closely related compounds completely blocked the thyroxine effect on oxygen uptake. L-Tryptophan reduced ammonia nitrogen accumulation in control and thyroxine vessels by one half. D-Tryptophan and DL-kynurenine had little effect on the controls but decreased the ammonia values in thyroxine vessels one third. The presence of L- or D-tryptophan resulted in glucose accumulation of only 10-20% of that obtained in their absence. DL-Kynurenine reduced the amount of glucose by about 50%. With DL-Kynurenine and D-tryptophan, oxygen consumption was lower in the thyroxine vessels than in controls, a reversal of the usual effect. A similar reversal was seen in the glucose and ammonia nitrogen production. Addition of the tryptophans or DL-kynurenine to the tissue without proline inhibited the thyroxine effect on oxygen consumption. With D-tryptophan and DL-kynurenine there was the complication that the inhibiting amino acids served as substrates, increasing ammonia production. DL-kynurenine reduced the already low endogenous glucose accumulation, but D-tryptophan did not change it. L-Tryptophan lowered ammonia but had no effect on the glucose. (Supported by Grant A-1545, USPHS).

THE IN VITRO EFFECTS OF THYROXINE ON RAT KIDNEY SLICE METABOLISM OF PROLINE. R.W.Hanson*, R.H.Lindsay* and S.B.Barker. (introduced by R.S.Teague). Dept. of Pharmacology, Univ. of Ala. Med. Center, Birmingham 3, Ala.

Previous studies showed that thyroidectomized rat kidney slices incubated in a Ringer-proline medium synthesized considerable amounts of glucose. With added thyroxine (T_4) the amount of glucose found slightly exceeded that of the controls when incubated at 37°C. When the slices were incubated for 1.25 hours at 37°C for each of 3 consecutive days and the remainder of the time at 5°C. the amount of glucose found in the T_4 vessels greatly exceeded that of the controls. Similar differences existed in the oxygen consumption values as well as in glutamic acid and ammonia nitrogen levels. From 60 to 103% of the proline nitrogen was recovered as glutamic acid plus ammonia nitrogen, the more complete recoveries occurring after 6 to 9 hours of incubation at 37°C. Of the total proline nitrogen recovered, ammonia represented about 85%, the remainder being glutamic acid. Following incubation with universally C-14 labeled proline, large quantities of radioactivity were recovered as C^*O_2. Chromatographic studies of the incubation medium showed only three radioactive spots corresponding to proline, glucose and glutamic acid.

NEUROPHARMACOLOGY II

Beaumont Lecture Hall, Memorial Building

A MICROCONNECTOR FOR CHRONIC ELECTROGRAPHIC STUDIES IN THE CAT. Lloyd B. Witkin, Robert Moore and Eugene O'Keefe (intr. by A.J. Plummer). Research Dept., CIBA Pharmaceutical Products Inc., Summit, N. J.

A microconnector housed in a stainless steel jacket with easy and rigid (screwless) attachment to the skull was designed in order to achieve preparations with reasonably long life expectancies for neuropharmacological studies in the unanesthetized animal. Nine coded beryllium-copper pins have been spun into a circular wafer of glass epoxy (G-11) with exposed lengths of 5 mm and with their other ends attached to color coded Kel-F coated wire. This unit was then spun into a stainless steel cylinder 1 cm long and 1 cm in diameter so that the pins were flush with the top of the cylinder. Six holes (2 mm diam.) near the base of the unit were used to bring out the wires. Six stainless steel nails (2 mm long) driven into the skull and secured to the base of the unit are used for attachment to the skull after which the entire inner base of the unit is further sealed into the skull with dental cement. After implantation in the cat, the unit protrudes less than 0.5 cm above the skin line. The operative procedure and details of construction of the connector will be discussed.

CEREBRAL SYNAPTIC DRUG ACTIONS IN THE ACUTE, NON-ANESTHETIZED PREPARATION. E. Ross Hart, Thomas O. Wilson* and Amedeo S. Marrazzi. Veterans Administration Research Laboratories in Neuropsychiatry, Pittsburgh 6, Pa.

The evoked potential, stabilized by light anesthesia, has served us well in studying cerebral synaptic function in cat transcallosal, cortico-cortical and retino-geniculate-cortical pathways. Besides other obvious drawbacks, anesthesia makes it difficult to distinguish between simple stimulation and an analeptic component exhibited only during anesthesia. Curarizing agents can substitute for anesthesia by immobilizing and thereby at the same time effecting the reduction in afferent inflow essential to stabilizing the evoked cortical responses. In this way we have been able to show that the action of cerebral synaptic inhibitors, like serotonin, is essentially unaltered by anesthesia and that stimulants like strychnine and pentamethylenetetrazol can exercise their typical actions in the absence of anesthesia.

REACTIVATION BY PAM OF BRAIN CHOLINESTERASE INHIBITED BY PARAOXON. Philip Rosenberg (intr. by S.C. Wang) Dept. of Neurol., Coll. of P. &S., Columbia U., N.Y.

For understanding the mechanism of alkylphosphate poisoning and the antidotal effects of 2-PAM it is important to know whether PAM penetrates the blood brain barrier and reactivates phosphorylated acetylcholinesterase in the brain. Observations by other workers have been either negative or inconclusive. Approximately LD_{20} doses of paraoxon (0.15 mg/kg) were injected intravenously into rabbits with or without treatment by PAM (25-250 mg/kg). A new procedure of chloroform extraction was used for removal of extracellular paraoxon; esterase activity following extraction was determined in various parts of the brain. A significant increase in enzyme levels after PAM was found in cerebral cortex and cerebellum, a greater increase in pons and medulla including the region of area postrema. No difference was observed whether PAM was injected 1 or 5 hrs. after paraoxon, indicating actual intracellular reactivation of the enzyme, since the circulation must have removed after 5 hrs. most of the extracellular alkylphosphate. The results suggest that PAM penetrates the blood brain barrier in sufficient amounts to cause marked reactivation of inhibited cholinesterase.

THE SYNERGISM OF 2-PAML AND TMB-4 AS ATROPINE ADJUNCTS IN GB POISONING. JOHN F. O'LEARY, ANNE M. KUNKEL*, AND AILI H. OIKEMUS*. PHARMACOLOGY BRANCH, CHEMICAL WARFARE LABS., ARMY CHEMICAL CENTER, MD.

IN VIEW OF RECENT EVIDENCE THAT 2-FORMYL-1-METHYLPYRIDINIUM IODIDE OXIME (2-PAM) HAS A WEAK DEPOLARIZING ACTION AT THE NEUROMUSCULAR JUNCTION (WILLS, ET AL., PROC. SOC. EXPT'L BIOL. & MED. IN PRESS), AND THAT 1,1'-TRIMETHYLENE BIS (4-FORMYLPYRIDINE BROMIDE OXIME (TMB-4) NOT ONLY LACKS SUCH DEPOLARIZING ACTION BUT INSTEAD POSSESSES A CURARE-LIKE OR COMPETITIVE BLOCKING ACTION (BAY, FED. PROC. 18:366, PART I, 1959), EXPERIMENTS WERE CONDUCTED TO EXPLORE THE ADJUNCTIVE EFFICACY OF A MIXTURE OF THESE TWO TYPES OF COMPOUNDS AS AN ANTAGONIST TO GB (SARIN, ISOPROPYL METHYLPHOSPHONOFLUORIDATE) IN THE PRESENCE OF ATROPINE. IN PLACE OF THE IODIDE SALT 2-PAM, THE MORE SOLUBLE LACTATE SALT (PREPARED BY KONDRITZER ET AL., ARMY CHEMICAL CENTER, MD.), 2-PAML, WAS USED IN THE MIXTURE. THE EFFECTS OF THE USE OF THIS MIXTURE ON THE LD_{50} OF GB IN RABBITS, INVOLVING VARIOUS ROUTES OF ADMINISTRATION OF BOTH GB AND TREATMENT COMPOUNDS, WERE DETERMINED. THE RESULTS INDICATED THAT THE MIXTURE OF ATROPINE AND THE TWO OXIMES RAISED THE INTRAVENOUS LD_{50} VALUE OF GB SOME 300 FOLD, WHEN GIVEN INTRAVENOUSLY 30 SECONDS AFTER GB. THIS EXCEEDED BY AT LEAST 5 TIMES THE FIGURE OF GB LD_{50} ATTAINABLE BY ANY SINGLE ADJUNCTIVE OXIME TESTED, INCLUDING TMB-4. BY OTHER ROUTES OF ADMINISTRATION, THE GREATER EFFECTIVENESS OF THE MIXTURE WAS LESS PRONOUNCED, BUT NONETHELESS EVIDENT.

THE THERAPEUTIC INDEX OF HEXAFLUORODIETHYL ETHER (INDOKLON) AND ITS MODIFICATION BY RESERPINE AND IPRONIAZID. Edward B. Truitt, Jr. and Ethel M. Eberberger*. Dept. of Pharmacology, Univ. of Maryland Med. School, Baltimore, Md.

Therapeutic indices (T.I.) for hexafluorodiethyl ether (HFE) have been derived from measurements of clonic and tonic convulsions and death on an all-or-none basis when the drug was administered intraperitoneally, intravenously and by inhalation to rats and mice. By the I.P. route of administration the T.I. of HFE significantly exceeds that for pentylenetetrazol (PTZ). Intravenously the T.I. of both HFE and PTZ are smaller and HFE the safer of the two. By inhalation HFE exhibits a wide margin of safety and lethal effects are induced with difficulty.

Reserpine does not affect the threshold for a clonic convulsion by HFE, but it does cause an earlier appearance of preconvulsive myoclonic jerking. It also increases the frequency of tonic extensor convulsions and deaths. Iproniazid antagonizes these latter actions of reserpine to a limited degree. These results will be discussed in relation to the effects of reserpine and iproniazid on brain constituents. (Supported by USPHS Grant MY-2540)

EFFECT OF SEX HORMONES ON ELECTROSHOCK SEIZURE THRESHOLD AND ON GLYCOGEN AND ELECTROLYTE DISTRIBUTION IN BRAIN OF RATS. Dorothy E. Woolley* and Paola S. Timiras, Dept. of Physiology, Univ. of California, Berkeley, California.

The effects on brain excitability of estradiol dipropionate, progesterone, testosterone propionate and methylandrostenediol, alone or in combination, were measured by the electroshock seizure threshold (EST) test. Male adult rats received s.c. 0.5 mgm/100 gm B.W. of the hormones per day during 20 to 27 days. EST changes were not observed in rats injected with the male hormones or with progesterone alone. Estradiol markedly increased brain excitability as indicated by a progressively significant fall of the EST of 3%, 14% and 25% after 2, 4 and 20 days of treatment, respectively. Brain excitability was also markedly increased when estradiol and progesterone were injected together, but the rate of increase was slower in time than with estradiol alone: EST changes were absent after 4 days of treatment and an EST fall similar in magnitude to that of the estradiol-injected rats was reached only after 20 days. Blood glucose, brain glycogen and Na,K and Cl concentrations in brain and plasma were determined and correlated with the corresponding changes in brain excitability: the results will be reported.

DENERVATION SUPERSENSITIVITY IN UNDERCUT CORTEX STUDIED BY MEANS OF CHRONICALLY IMPLANTED ELECTRODES. Lawrence Halpern and Seth Sharpless (intr. by W. W. Douglas). Department of Pharmacology, Albert Einstein College of Medicine, New York City.

Hyperkinetic abnormalties and altered CNS functions after experimentally induced lesions have been attributed to Cannon's Law of Denervation (Drake and Stavraky, J. Neurophysiol., 1948, 11, 229; Jenkner and Ward, A. M. A. Arch. Neurol. & Psychiat., 1953, 70, 489). The present report deals with the time course of the appearance of an increased duration of the afterdischarge elicited by direct cortical stimulation. Stimulating and recording electrodes embedded in plastic were implanted over a chronically isolated slab of suprasylvian cortex in cats. Similar electrode assemblies were implanted over the homologous area on the opposite hemisphere and over adjacent intact areas. The electrocorticogram was recorded at frequent intervals during the following weeks, and the threshold and duration of the afterdischarge produced by repetitive stimulation was measured. Supersensitivity in the isolated slab was revealed by an increased duration of afterdischarge and a decreased threshold, which developed within three weeks after the operation. The homolgous area on the opposite hemisphere also showed some increase in sensitivity when compared with adjacent, intact cortex.

CLASSIFICATION OF CNS DRUGS BY A MOUSE SCREENING BATTERY. J. W. Bastian (intr. by Dr. C. D. Proctor) Armour Pharmaceutical Company, Kankakee, Illinois.

An arbitrary classification of a number of currently used CNS depressant drugs has been obtained by determination of differential effectiveness on 6 measures of drug activity (Metrazol threshold, % block of extensor tonus, time to death following Metrazol convulsion, spontaneous running activity, ataxia and body temperature). All 6 endpoints are evaluated in each animal to obtain best comparison of differential effects. Drugs are administered per os in 1% pectin, and activities are measured routinely at 30, 60 and 120 minutes, or at other times to include peak action. Marked differences in specificity were found for the following drugs among 26 tested: NaBr, styramate, chlorpromazine, diphenylhydantoin, phenobarbital, methyprylon, ethchlorvynol and zoxazolamine. Other drugs exhibit similar or intermediate specificities or show no activity on any of the endpoints employed. Compounds which elevate Metrazol threshold often increase spontaneous running activity and are usually known to cause hypnosis at high doses in humans. Drugs which lower body temperature tend to delay time to death following Metrazol convulsion and usually depress spontaneous running activity.

PHARMACOLOGIC STUDIES OF TIGAN, A SPECIFIC ANTI-EMETIC. E. F. Keith, R. E. Bagdon and B. Koechlin. (intr. by W. B. Schallek). Dept. of Pharmacology, Roche Laboratories Division, Hoffmann-La Roche Inc., Nutley 10, N. J.

Tigan hydrochloride, a specific anti-emetic, when administered intravenously to the dog in doses several times the anti-emetic dose failed to show anti-histaminic activity. At extremely high doses there was a reduction in the depressor response to the administration of histamine. To determine whether this response was peculiar to the dog, studies were undertaken using the guinea pig as the experimental animal. Histamine was administered to the animals by the intracardiac route. The PD_{50} for lethality against 1 & 7 lethal doses of histamine were determined for chlorpromazine. Tigan was inactive. CFN rats were given Tigan in the diet at doses of 40, 80 and 160 mg./kg. for 24 weeks. The animals on 40 and 160 mg./kg. were paired and bred beginning in the 17th experimental week. Tigan showed no deleterious effect on growth, hematopoietic and other tissues, or reproduction at these levels. Blood levels of Tigan have been determined in the human at 100 and 300 mg. administered by the oral route. These results will be discussed.

NEUROPHARMACOLOGICAL COMPARISON OF ATROPINE, SCOPOLAMINE, BENACTYZINE, DIPHENHYDRAMINE AND HYDROXYZINE. Richard P. White and Louis D. Boyajy*. Division of Pharmacology, University of Tennessee Medical Units, Memphis.

The drugs studied were given i.v. and induced an EEG synchronous pattern without concomitantly depressing behavior in rabbits. High doses of atropine(60 mg/kg) or scopolamine(30 mg/kg) did not sedate or excite, but high doses of diphenhydramine, benactyzine, and hydroxyzine usually caused excitement. Low doses of scopolamine(0.5 mg/kg) blocked the usual EEG effects(arousal) of 0.2 mg/kg of physostigmine and 5 mg/kg of d-amphetamine, though the latter drug provoked behavioral excitation. Similar results were obtained with benactyzine. Atropine in 3 mg/kg doses failed to block the effects of 0.2 mg/kg of physostigmine but did the effects of amphetamine(5 mg/kg). In 5 mg/kg doses, however, atropine also blocked physostigmine. Diphenhydramine(5 mg/kg) usually blocked amphetamine but not physostigmine and resembled the effects seen with lower doses of atropine. Hydroxyzine(5 mg/kg) was the only drug which did not block the EEG effects of low doses of physostigmine or amphetamine and did not cause mydriasis. Thus, scopolamine was at least 10 times more effective than atropine in antagonizing the EEG effects of physostigmine; benactyzine was similar to scopolamine. The actions of hydroxyzine, in the doses employed, was the least atropine-like. (Supported by U.S.P.H.S. Senior Research(SF-279) grant and U.S.P.H.S. grant No. A-2200.

ACETYLCHOLINE: ITS SIGNIFICANCE IN CONTROLLING THE CILIARY ACTIVITY OF HUMAN RESPIRATORY EPITHELIUM IN VITRO. Gunter Corssen and Charles R. Allen (intr. by Russell A. Huggins), Dept. of Anesthesiology, University of Texas Medical Branch, Galveston, Texas.

Explants of human respiratory epithelium cultured in a plasma clot tend to round up and to form rotating globes which can be employed in perfusion chambers for the study on the effect of various chemicals on ciliary activity. Perfusion of acetylcholine hydrochloride solutions at 0.1 per cent to 1.0 per cent concentration invariably increased rotatory movement of the cell cluster. Bathing the epithelial explant in 0.05 per cent to 0.1 per cent eserine salicylate solutions prior to the perfusion with acetylcholine hydrochloride markedly enhanced the acetylcholine effect on ciliary activity. Perfusion of atropine sulfate solutions at concentrations of 0.1 per cent and stronger resulted in a short lasting stimulatory effect followed by progressive reduction of rotatory motion. The depressant action of atropine sulfate was observed to be counteracted by acetylcholine hydrochloride at 0.5 per cent concentration. The behavior of the rotating ciliated cell mass exposed to the various substances appears to be consistent with the assumption that acetylcholine plays the key role in initiating and maintaining the contractile mechanism of ciliary motion.

RESPONSE OF THE VENOUS SYSTEM TO INTRAVENOUS ACETILCHOLINE. H.J. Bartelstone (intr. by S.C. Wang) Dept. of Pharmacology, College of Physicians and Surgeons, Columbia Univ., New York.

Acetylcholine, in small doses, applied directly to veins has been shown to produce dilatation of these vessels. However, the reaction of the venous system to small doses of acetylcholine, i.v., is constriction rather than dilatation because of predominant reflex effects. Evidence was obtained from dogs during periods in which the venous system was isolated by transient occlusion of the thoracic inferior vena cava and the descending aorta (for technique, see Bartelstone, Fed. Proc., 18:8, 1959). The i.v. injection of acetylcholine, 1-5 γ/kg., produced a fall in arterial pressure which was followed, in 4-6 seconds, by an increase in the volume of blood entering the central veins. Reflex response to the arterial pressure fall produced peripheral venoconstriction while the arterial system was still directly dilated by the acetylcholine. Reflex constriction of the peripheral venous bed overwhelmed the direct action which the greatly diluted and partially hydrolyzed dose of acetylcholine may have had on the venous system. The increase in venous return was independent of direct cardiac or arterial influences. Interruption of baroreflex arcs prevented the increase in venous return following injection of acetylcholine. The response of the venous system to intravenously injected vasoactive drugs should not be presumed to be qualitatively similar to the response of the arterial system. (Supported by USPHS B31.)

MYDRIATIC AND INTRAOCULAR TENSION LOWERING PROPERTIES OF THE HEMICHOLINIUM (HC-3). J.P. Long, M.F. Armaly* and R.D. Whinery*. Departments of Pharmacology and Ophthalmology, College of Medicine, State University of Iowa, Iowa City, Iowa.

The following pharmacological properties of HC-3 in relation to the eye will be discussed: (a) Instillation of HC-3 as a 1% solution in 1/1000 aqueous zephiran in the cats' eyes produces maximal mydriasis in about one hour followed two to three hours later by lowering of the intraocular tension as measured by the Schiotz tonometer. The contralateral eye is unaffected. Mydriasis and reduced tension are readily antagonized by cholinergic agents: (b) Systemic administration of HC-3 produces mydriasis in one hour in a postganglionic stimulated ciliary nerve preparation; (c) HC-3 is about 1/1000th as active as atropine as a mydriatic agent in mice. The time-effect curves are similar: (d) No cholinesterase inhibiting or activating properties were noted in the cat's iris or ciliary body following HC-3.

RELATIONSHIPS BETWEEN THE CHEMICAL CONSTITUTION AND BIOLOGICAL RESPONSE OF D(-)-, L(+)- AND DL-LACTOYLCHOLINES, AND RELATED COMPOUNDS. B. V. Rama Sastry*, C. C. Pfeiffer and A. Lassle*. Dept. of Pharmacology, Emory University, Atlanta, Georgia.

The position of the asymmetric carbon in atropine (DL-hyoscyamine) and the high isomeric ratio of D- and L-hyoscyamine in pharmacological studies suggest an asymmetric center in the α-position to the carbonyl group of an acetylcholine-like neurohumor (Pfeiffer, Int. Rev. Neurobiol., 1: 195, 1959). The synthesis of L and D choline esters (J. Org. Chem., 23: 2005, 1958) with such asymmetric centers was therefore undertaken. The pharmacological effects of D(-)-, L(+)- and DL-lactoylcholines, DL-glyceroylcholine and DL-lactoyl-DL-(β-methylcholine) have been determined in the anesthetized dog before and after atropine.- The nicotinic activity of DL-lactoylcholine proved to be equivalent to that of acetylcholine (ACh); the D-isomer was 1.5 times more, and the L-isomer was 3.5 times less potent than ACh. The lactoylcholines were considerably less active than ACh in their muscarinic action (DL, 1/250; D(-), 1/100; L(+), 1/1100). The isomeric ratios (D/L) indicate (5 for nicotinic and 11.3 for muscarinic) that asymmetry in the acyl component of choline esters may affect significantly their pharmacodynamic properties. The relative rates of hydrolysis of the new choline esters by human plasma cholinesterase, in vitro, seem to support the pharmacological findings.

AN INVESTIGATION OF THE EFFECT OF AUTONOMIC DRUGS ON THE IRIS. Donald R. Bennett, Kent R. Hornbrook*, and Thomas Baun*. Dept. of Pharmacology, Univ. of Michigan, Ann Arbor, Mich.

The iris muscles are useful test objects for autonomic drug-receptor studies. However, parenteral administration of drugs produces both direct and centrally mediated reflex effects on one or both muscles. Conversely, isolated iris preparations have the usual disadvantage of such methods. In order to obviate some of these problems, drugs have been injected into the posterior chamber of the eye. Unanesthetized rabbits are employed. With a few modifications, the guinea pig may also be utilized. Pupil size is determined with a camera. Volume of fluid injected is limited to .05 ml through a #30 gauge needle. Drugs are diluted in normal saline. Injection of .05 ml saline produces little alteration of pupil size compared to normal alteration of pupil size in uninjected control eyes. A marked mydriasis, persisting for approximately 90 minutes, is produced by 2.0 mcg of l-epinephrine HCl. Dose response relationships for the d and l isomers of epinephrine, norepinephrine, and isoproterenol have been determined and will be presented. Data on the effectiveness of parenterally administered dibenzyline and dichloroisoproterenol to prevent the responses of the above adrenergic drugs will also be presented.

A STUDY OF PRESYNAPTIC SLOW POTENTIALS IN VIRUS-INFECTED SYMPATHETIC GANGLIA OF THE RAT. Jacob Zabara* and John Dempsher. Dept. of Pharmacology and Institute of Neurological Sciences, University of Pennsylvania Med. School, Philadelphia, Pa.

Two kinds of spontaneous potential changes were observed in excised rat superior cervical ganglia following infection with pseudorabies virus, a slowly changing potential, the slow potential, on which was superimposed a rapidly changing potential, the spike. Presynaptic and postsynaptic slow potentials were discharged simultaneously and synchronously, but in advanced infections when the postsynaptic slow potential was absent, a presynaptic slow potential might still be present. Physostigmine and ACh initially increased the size of the presynaptic slow potential, then decreased it. Thiosemicarbazide increased the size of the presynaptic slow potential. Tubocurarine, gamma aminobutyric acid, adrenaline and noradrenaline decreased the size of the presynaptic slow potential. It is suggested that the presynaptic slow potential originated in the presynaptic nerve endings, served as a focus for depolarization of the preganglionic axon and represented the electrical event accompanying interaction between excitatory and inhibitory systems at the presynaptic nerve endings.

THE GANGLIONIC BLOCKING PROPERTIES OF 2-(3-PENTYL)IMIDAZOLINE (WL-17) AND 2-(3-PENTYL)IMIDAZOLE (WL-64). Frederick F. Cowan (intr. by T. Kopoanyi). Dept. of Pharmacology, Georgetown U. Med. School, Washington, D. C.

Two structurally related compounds, 2-(3-pentyl)imidazoline (WL-17) and 2-(3-pentyl)imidazole (WL-64), were shown to possess ganglionic blocking properties characterized by a moderate order of potency and duration of action. WL-17 and WL-64 inhibit the contractions of the nictitating membrane in the chloralosed cat induced by preganglionic cervical sympathetic trunk stimulation without markedly affecting those brought about by postganglionic stimulation. Both compounds inhibit the vasodepression elicited by vagal stimulation and the vasopressor responses induced by nicotine, carotid occlusion and large doses of acetylcholine in the atropinized dog or cat. The vascular response to epinephrine is potentiated, whereas those to small doses of acetylcholine and histamine are unaltered. Nictitating membrane contractions of the atropinized, chloralosed cat were elicited by close arterial injection of acetylcholine and potassium chloride into the superior cervical ganglion. Intravenous or close arterial injection of WL-17 or WL-64 cause a transient abolition of the acetylcholine contractions, but no alteration of the potassium chloride contractions. Intraduodenal administration of WL-17 and WL-64 shows that both drugs are readily absorbed. (Supported in part by the Schering Corporation Fellowship.)

EFFECTS OF BLOCKING AGENTS ON SYMPATHETIC AND PARASYMPATHETIC GANGLIONIC ACTION POTENTIALS. F. Alonso de Florida,* J. Cato,* L. Ramírez* and E. G. Pardo. Depts. of Physiology and Pharmacology, Escuela Nacional de Medicina, U.N.A.M. México, D.F.

Quantitative differences between the actions of ganglionic blocking agents on sympathetic and parasympathetic structures have often been reported. The comparisons have been made using effector response as criterion of the ganglionic blocking action. The results lend themselves to diverse interpretation in view of the possibility of direct action on the effectors, of non-linearity of the relation between effector and ganglionic response and of differences arising from the use of varying frequencies of activation. The effects of continuous infusions of tetraethylammonium, hexamethonium, d-tubocurarine, ethyl-methyl-iso-octenyl-amine and diphemanil on transmission at the superior cervical ganglion and at the ciliary ganglion were studied measuring the postganglionic action potentials resulting from single maximal stimuli applied to the preganglionic nerves. The results do not confirm the reported differences in ganglionic sensitivity. Additionally, most of the drugs tested showed initial facilitation of ganglionic transmission.

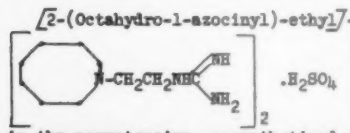
AUTONOMIC EFFECTS OF TREMORINE. Alexander H. Friedman* and Cedric M. Smith. Dept. of Pharmacology, Univ. of Illinois Coll. of Medicine, Chicago, Ill.

Tremorine, 1,4-dipyrrolidino-2-butyne, has been reported (Everett, Nature, 177: 1238, 1956) to produce the parasympathomimetic effects of miosis, profuse salivation, diarrhea, and bradycardia, in addition to tremor, asthenia, and rigidity. The purpose of this investigation was to localize and define the nature of Tremorine's parasympathomimetic effects. The IC50's of Tremorine for the inhibition of true (bovine erythrocyte) and pseudo (rat mucosa) cholinesterase were 1.4×10^{-5} and 5×10^{-6} as compared with 6.6×10^{-9} and 1.7×10^{-9} M., respectively, for neostigmine. The salivation produced by Tremorine was inhibited by tetraethylammonium or atropine but it was not altered by section of the chorda tympani and cervical sympathetic nerves. Tremorine (20 mg/kg, i.p.) produced a marked transient mydriasis in mice which reached a peak in 15 minutes and which decreased to control levels in about one hour. This mydriasis was antagonized by carbachol (1.5 mg/kg, s.c.) pretreatment; it was unaffected by pretreatment with dibenzyline; the mydriatic effects of Tremorine and hexamethonium were additive. Thus, it is postulated that these effects of Tremorine are the result of stimulation and/or inhibition at autonomic ganglia. (Supported in part by Grant B-973, USPH.)

THE EFFECT OF DRUGS UPON THE PRODUCTION OF GASTRIC ULCERS BY THE RESTRAINT TECHNIC. David A. Brodie and Harley M. Hanson.* Merck Institute for Therapeutic Research, West Point, Pa.

Male Holtzman rats (50-100 gm.) were restrained by molding steel window screen tightly around the rat and securing the screen with wire staples. The ulcers produced by this stress procedure occurred only in the fundus of the stomach. The rats were starved 48 hours prior to a restraint period of 4 hours, and the percentage of animals with ulcers in the control groups was 69% (55-83). All drugs were injected intraperitoneally at the time of restraint. Atropine sulfate, 6 mg./kg., lowered the incidence of rats with ulcers to 25%, while the same dose of diphenmethanil and propantheline reduced the ulcer incidence to 37 and 14%, respectively. Atropine sulfate, at a dosage of 1.5 mg./kg., reduced the incidence of gastric ulcers to 50%, while scopolamine methiodide at the same dose reduced the incidence of gastric ulcers to 0%.

PHARMACOLOGY OF /2-(OCTAHYDRO-1-AZOCINYL)-ETHYL/-GUANIDINE SULFATE (SU-5864). R. A. Maxwell, A. J. Plummer, F. Schneider,* H. Povalski,* A. I. Daniel.* Research Dept. Ciba Pharmaceutical Products Inc., Summit, N. J.



/2-(Octahydro-1-azocinyl)-ethyl/-guanidine sulfate (Su-5864) profoundly lowers the arterial pressure of unanesthetized neurogenic and renal hypertensive dogs. It has a slight hypotensive action in the normotensive unanesthetized and anesthetized dog. Su-5864 is likewise a potent antagonist to the pressure responses elicited by 1) bilateral occlusion of the carotid arteries, and 2) injection of high doses of amphetamine. These actions last for periods ranging from 4 days to 3 weeks following single intravenous injections. The first several hours of Su-5864 action are characterized by sympathetic-like actions. During the rest of the course of action of this drug sympathetic atony is prevalent. Only a transient blocking effect on sympathetic ganglia and on efferent parasympathetic transmission occurs following Su-5864. At the same time the arterial system and the nictitating membranes are hyperresponsive to injected norepinephrine during this period of sympathetic atony. It is concluded that Su-5864 chronically interferes with the release and/or distribution of the neurohumoral transmitter at the sympathetic neuromuscular junction.

HEMODYNAMIC EFFECTS OF S.K.F. 6890. G. G. Rowe, C. A. Castille*, J. E. Clifford*, G. M. Maxwell* and C. W. Crumpton. Depts. of Medicine and Pediatrics and the Cardiopulmonary Research Lab. of Univ. of Wisc., Madison, Wisconsin.

S.K.F. 6890 has been tested in 10 dogs anesthetized with 3 Mg./Kg. of morphine Sub-Q followed in one hour by 0.25 ml./Kg. of a 50-50 mixture of Nembutal and Dial-Urethane I. V. Cardiac output (Fick) and coronary blood flow (N_2O Method) were determined before and after 5 Mg./Kg. of the drug I. V. Significant reductions occurred in pressure in the femoral ($p<0.02$) and pulmonary ($p<0.05$) arteries and the right atrium ($p<0.05$). O_2 consumption was unchanged, but the A-V O_2 difference increased ($p<0.01$) as did the A-CSO_2 ($p<0.001$) and there was a decrease in cardiac output ($p<0.05$) and coronary blood flow ($p<0.001$). The cardiac efficiency index decreased ($p<0.05$). Both left and right ventricular work decreased ($P<0.01$) but there was no significant change in systemic or pulmonary vascular resistance. Coronary vascular resistance increased. The hemodynamic effects of this compound and those of hexamethonium and mecamylamine are strikingly similar.

CENTRAL ACTIVITY OF CERTAIN HYPOTENSIVE AGENTS. J. P. Buckley, W. J. Hudak*, R. K. Bickerton*, and W. J. Kinnard Jr.*. Dept. of Pharmacology, University of Pittsburgh School of Pharmacy, Pittsburgh.

A dog cross-circulation preparation was developed and utilized to determine the central activity of certain hypotensive agents. The method used was a modification of the open chest technique plus the occlusion of the venous sinuses and vertebral arteries. Circulation to the recipient's head was established via the recipient's two common carotid arteries and external jugular veins, and the corresponding left vessels of the donor. Ten microcuries of I^{131} (radio-iodinated serum albumin) was administered into the recipient's arterial inflow. Blood samples were obtained from the femoral veins of both dogs periodically and the amount of radioactivity determined. The mean per cent radioactivity of the recipient was less than 3% in 3 hours (22 experiments). Experimental hypotensive agents were administered into the recipient's arterial inflow. The following compounds demonstrated central hypotensive effects: Betadimethylaminoethyl-N-methylpipecolinate, dimethobromide, iproniazid, phenylisopropylhydrazine, and syrosingopine. (Supported by grant H-3475, National Heart Institute; and Hoffmann-LaRoche Inc., Nutley, N.J.).

VASOMOTOR RESPONSES TO CENTRAL VAGAL STIMULATION IN VARIOUS SPECIES BEFORE AND AFTER HYPOTENSIVE DRUGS. J. R. Cummings and J. L. Grace, Jr. (intr. by W. D. Gray). Experimental Therapeutics Research, Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

In normotensive dogs with vagi intact, doses of 1-5 mg/kg hydralazine failed to produce consistently a marked reduction in blood pressure. The same doses, however, always elicited a sustained and reproducible hypotension in vagotomized dogs and in normal and vagotomized rats. As a result of our experience with hydralazine and other hydrazines, rauwolfia alkaloids and ganglionic blocking agents, the effect of central vagal stimulation (CVS) on arterial blood pressure was studied in several species of normotensive animals. The central end of either vagus was stimulated with a square wave impulse and the vasomotor response before and after administering a hypotensive agent was recorded. In dogs, CVS resulted in a vasopressor response which was potentiated by hydralazine and was blocked by reserpine. In rats, rabbits and cats, CVS produced a fall in arterial blood pressure. Hydralazine and reserpine partially or completely blocked the CVS-vasodepressor effect in rats and rabbits and usually reduced the response in cats. The effect of phenylisopropyl hydrazine (JB 516) and hexamethonium on the CVS vasomotor response was also studied.

EFFECT OF GUANETHIDINE (SU-5864) ON TISSUE CATECHOLAMINES Herbert Sheppard and Joseph Zimmerman (intr. by A.J. Plummer) Research Dept., CIBA Pharmaceutical Products Inc., Summit, N.J.

White rats were administered guanethidine, [2-(octahydro-1-azocinyl)-ethyl] guanidine sulfate, intraperitoneally at a dose of 15 mg/kg. Animals were sacrificed by decapitation, and brain, heart, spleen and adrenals removed for analysis of catecholamines by a modification of the method of Weil-Malherbe and Bone. No effect was observed on the catecholamine levels of the tissues of the rats sacrificed 24 hours after administration of the drug. However, heart and spleen catecholamine levels were reduced almost 50 per cent in the rats sacrificed two hours after administration of the drug. No effect was observed on adrenal or brain levels at that time. The results of a study of the time course of depression of catecholamines in heart and spleen will be presented in detail and an attempt will be made to relate these changes to the pharmacological action of the drug.

THE EFFECT OF 3-OH TYRAMINE UPON THE SYSTEMIC, PULMONARY AND CORONARY HEMODYNAMICS AND METABOLISM OF THE INTACT DOG. G. M. Maxwell*, G. G. Rowe, C. A. Castille*, C. W. Crumpton & J. E. Clifford*. Cardiovascular Lab., Univ. of Wisc., Madison, Wisc.

Eight dogs were premedicated with Morphine Sulphate (3 mgm./Kgm. S. C.), and anesthetized with Dial-urethane-Nembutal (50: 50 mixture; 0.25 cc./Kg./I. V.). Cardiac output (Fick) and coronary blood flow (N_2O Fick), were measured before and after the infusion by mechanical pump of 3-OH Tyramine, (50 gamma/Kg./minute over 30 minutes). The following statistically significant ($p<0.05$) results were obtained: Increases in cardiac output (+31%), stroke volume, mean femoral B.P., pulmonary arterial B. P., left ventricular work, left ventricular stroke work, right ventricular work (+100%), and total pulmonary resistance (+22%). Coronary blood flow increased from 79 to 531 cc./100 gm./min.; coronary vascular resistance (calc.), decreased from 1.6 to 0.5 units. Coronary sinus oxygen content increased from 4.6 to 11.0 vols. %. Cardiac oxygen extraction decreased. The cardiac metabolic rate for oxygen increased, (10.3 to 39.1 ccs./100 gm./min.), as did cardiac oxygen consumption determined directly. Mechanical efficiency decreased from 23% to 15%.

THE EPHEDRINE-LIKE ACTION OF 2-AMINO-2-METHYLPROPANOL (2-AMP). G. F. Kiplinger*, F. Attinger*, and C. J. Kensler. Dept. of Pharmacology and Experimental Therapeutics, Boston Univ. School of Medicine, Boston, Mass.

We have previously reported (Fed. Proc. 18:410, 1959) on the cardiovascular actions of 2-amino-2-methylpropanol (2-AMP). The compound was found to have a biphasic effect on the blood pressure of the anesthetized cat, producing first a depressor response followed by a pressor. The pressor effect could be eliminated by pretreatment of the animal with reserpine 24 hours prior to the experiment. Further evidence now indicates that the pressor effects of 2-AMP as well as the pressor effect of ephedrine can be blocked by SKF #5377-C (TM-10, choline 2,6-xylyl ether). Since it has been demonstrated that the pressor effect of ephedrine can also be markedly attenuated by reserpine pretreatment, it would appear that both ephedrine and 2-AMP exert their pressor effects by causing the release of a pressor substance.

A FUSED AMINO-OXAZOLINE SHOWING UNEXPECTED SYMPATHOMIMETIC ACTIVITY. Edward V. Dietrich (intr. by William M. Govier). Dept. of Pharmacology, McNeil Laboratories, Inc., Phila., Pa.

trans-2-Amino-3a,4,5,6,7,7a-hexahydrobenzoxazole fumarate (I) is a sympathomimetic having about 1/10 the potency of ephedrine. (I) is likewise distinguished in possessing much greater duration of action than that of ephedrine. The compound demonstrates tachyphylaxis without blood pressure reversal and its pressor effect is only partially blocked by dibenamine. Absorption is rapid by the intraduodenal route of administration. In the pentobarbitalized open-chest dog 5.0 mg/kg of (I) causes an increase in blood pressure with reflex bradycardia and an increase in the contractile force of the heart. Femoral blood flow studies show that a dose of 0.5 mg/kg intra-arterially produces a marked decrease in flow. Gross observation of rats revealed no CNS excitement with oral doses of 100 mg/kg and above, whereas, ephedrine at the same doses produced marked excitement for a prolonged period of time. Toxicity data will be presented in brief.

A COMPARISON OF CERTAIN PHARMACOLOGICAL PROPERTIES OF NYLIDRIN AND ISOXSUPRINE. William J. Kinnard Jr.*, Joseph P. Buckley, and Mario D. Aceto*. Dept. of Pharmacology, School of Pharmacy, University of Pittsburgh, Pittsburgh, Pa.

Chemical similarity prompted the comparative study of various cardiovascular properties of nylidrin and isoxsuprine. The effects of the agents were noted on the isolated cat heart using the Langendorff Technique. Nylidrin, in doses of 5 and 10 mcg. produced a greater increase in coronary flow and cardiac amplitude than did equal doses of isoxsuprine. Both compounds were tested on the turtle heart in situ. Auricular-ventricular conduction and contractility were depressed by doses of 0.5 to 2.0 mgm. The greatest effect of both compounds appeared to be on the auricles. Nylidrin and isoxsuprine induced electrocardiographic changes in the unanesthetized dog and the anesthetized cat. Blood flow studies were conducted in the anesthetized dog, utilizing the Shipley Rotameter and the Sanborn Viso-Cardiette, and arterial blood pressure was recorded simultaneously. The intraarterial injection of nylidrin and isoxsuprine in doses of 50 and 100 mcg./Kg. produced an elevation of femoral blood flow with little difference noted between the responses of the two drugs. Tachyphylaxis was noted throughout the course of the study. The influence of the drugs on the coronary and renal blood flow was also investigated. (Supported by a grant from U. S. Vitamin & Pharmaceutical Corp.)

THE USE OF DCI IN DIFFERENTIATION BETWEEN ADRENALINE AND NOR-ADRENALINE. Walter M. Booker, Austin Moore*, Mabel Robinson* and Estela Gonzalez*. Dept. of Pharmacology, Howard Univ. College of Medicine, Washington, D. C.

During the course of experimentation on the isolated perfused guinea pig heart as a biological assay method for adrenaline, it became apparent that DCI blocks adrenaline within two to three minutes after it (DCI) is administered to the heart preparation. The blocking of the positive inotropic action of adrenaline is often accompanied by a negative chronotropic and a negative inotropic response. During this time, nor-adrenaline is lowered in its positive inotropic action but is not blocked. A negative inotropic and chronotropic action under such state does not occur. Increasing the dose of adrenaline may overcome the blocking action of DCI, but the dose of adrenaline, unlike nor-adrenaline, must be raised many times. This differentiation, while present in low doses (0.0006 - 0.001 gamma) of the catechol-amines, is not as sharp at this dose range as when the concentrations are higher (0.05 - 0.1 gamma and above). Experiments are under way now studying variable doses of DCI and their effectiveness against adrenaline and nor-adrenaline.

THE DEPRESSOR AFTEREFFECTS OF NOREPINEPHRINE. Kenneth C. Back* and Harold A. Shoemaker. Research Center, Pitman-Moore Co., Indianapolis, Ind. and Dept. Pharmacol., University of Okla., School of Medicine, Oklahoma City, Okla.

The depressor effect of l-norepinephrine (NE) was produced by infusing dogs with doses of 3.3-4.2μg/kg/min for 4-5 hrs. Long-term infusion invariably showed two distinct effects: 1) The blood pressure rises precipitously, but then gradually falls below pre-infusion levels; 2) after discontinuing the infusion the blood pressure falls to an even lower level. Faradic stimulation of the cut peripheral vagus nerve, during and following infusion, indicated that the ganglionic blocking effect of NE was not a major factor in the development of the vasodepressor effects. Ephedrine and the antihistaminic drugs tripelennamine, pheniramine, and diphenhydramine augment the pressor effect of single and infused doses of NE but do not protect against the post-infusion hypotension. These drugs have been reported to be amine oxidase inhibitors. The antihistamines, phenindamine and antazoline, did not have these effects and are not amine oxidase inhibitors. Single doses of NE and ephedrine are capable of increasing the blood pressure following the infusion. In the debuffered dog, protoveratrine A is also capable of increasing the post-infusion blood pressure indicating that the cardiovascular system is still capable of vasoconstriction by both exogenous and endogenous pressor agents.

TOXICOLOGY
Room N-204, Memorial Building

EFFECTS OF SODIUM SELENITE ON SOME BLOOD CONSTITUENTS. Max Heinrich, Jr. Dept. Pharmacology, State University of South Dakota, Vermillion.

During earlier studies in which sodium selenite was administered to anesthetized dogs it was noted that acidosis developed late in the course of acute selenite poisoning. Respiratory stimulation occurred and was accompanied by variable changes in the blood carbon dioxide levels. This suggested that the acidosis was of metabolic origin. Hematocrits, venous pH, and plasma levels of sodium, potassium, calcium, protein, phosphate, pyruvate, and lactate were determined before, and at various intervals after, the intravenous administration of 0.1, 0.25, 1.0, and 2.0 mg/kg Se as sodium selenite to anesthetized dogs. No differences were noted between anesthetized and unanesthetized dogs receiving 2.0 mg/kg Se. Plasma sodium changes were inconstant. Calcium, phosphate, and protein alterations were dose-dependent. Hyperkalemia, hyperpyruvatemia, hyperlactatemia, decreased venous pH, and hemoconcentration were consistent findings regardless of the selenite dosage. Possible explanations and the relation of these findings to selenium toxicity will be discussed.

TOXICOLOGY OF THE WESTERN ATLANTIC PUFFER FISHES OF THE GENUS SPHOEROIDES, Edward Larson, Luis R. Rivas*, R. C. Lalone*, and Stuart Coward*. Ichthyological Laboratory and Museum, Dept. of Zoology, Univ. of Miami, Coral Gables, Fla.

Though the toxicity of the Pacific puffers have been studied by Halstead et al. (Hancock Foundation Publication #17, 1955) the Atlantic puffers have received little scientific attention. Extracts of the skin, gonads, liver and muscle were prepared and tested by the method suggested by Halstead et al. (loc. cit.). The skin and ovary have proven toxic in most cases whereas the liver, testes and muscle have proven non-toxic. The LD_{50} of the skin extract of Sphoeroides maculatus intraperitoneally in the mouse has been found to be about 0.14 cc. per 20 grams. From the symptoms produced, it appears that death is caused by convulsions due to anoxia. Several antidotes have been tried. Ephedrine, Metrazol, calcium gluconate, atropine and sodium succinate have not been too successful but pentobarbital offers some hope. In the turtle heart, vagal blockage is produced. In the anesthetized rat, skin extract of Sphoeroides maculatus produces an increase in blood pressure.

PHARMACOLOGY OF PARALYTIC SHELLFISH POISON. William D'Agaunno (intr. by A. J. Lehman). Div. of Pharmacology, Food and Drug Admin., Washington, D. C.

Earlier work with crude (10 Mouse units/mg) paralytic shellfish poison showed that one of the effects was a curarizing of the skeletal musculature. An attempt to elucidate this mechanism was deemed advisable since purification had been improved considerably (5500 M. U./mg.). Respiration was found to be depressed centrally with no curarization peripherally in animals by use of a diaphragm preparation. Among the effects observed on blood pressure was a 30-60 second delay in hypotensive response, which became progressively greater with repeated I. V. injections of 1γ/kg at 30 minute intervals. Acetylcholine, vagotomy, histamine and atropinization failed to alter this response. Indications were that NaCl exerted a protective effect. Responses in in vitro preparations were suggestive of a surface or ionic effect. Similarly in mice I. P. injection of 14γ/kg of the poison resulted in convulsions and death, symptoms not being unlike those caused by certain ions. A study using mice showed that 0.9% NaCl offered some protection, the time before death occurs being increased. At 280 mEq/L Na it was observed that pyruvate, bicarbonate, acetate and lactate reduced the deaths in mice from 86% to 8-12%; with chloride, succinate and glycerophosphate the results were 45-60%. Sodium glucuronate and citrate afforded little or no protection. The effects of these cations on respiratory and blood pressure responses to the poison are being determined.

A STUDY OF FACTORS INFLUENCING UREA HYDROLYSIS IN ANIMALS. Willard J. Visek, Donald M. Pearson and Leokadia Derkowska. (intr. by L. J. Roth). Dept. of Pharmacology, University of Chicago, Chicago, Ill.

Male Sprague-Dawley rats weighing 30 to 50 g were fed ad libitum for six weeks on diets containing soybeans plus methionine as a source of protein. During periods of four hours following subcutaneous injection of C-14 urea animals fed raw soybeans expired 2.70% of the administered C-14 in the form of $C^{14}O_2$ if fasted for 16 hours and 15.6% if not fasted. Corresponding values for animals fed autoclaved soybeans were 3.12 and 17.8; for animals fed raw soybeans plus 0.1% chlortetracycline 2.38 and 13.7, and for animals fed a ground laboratory ration (Rockland) 2.52 and 10.6. Ureolytic activities of the gastrointestinal tract plus contents expressed as mg. of urea split per g/dry matter were 23.7 for the small intestine and 90.1 for the large intestine for raw soybeans. Respective values for autoclaved soybeans were 11.6 and 83.5 and for raw soybeans plus 0.1% chlortetracycline they were 9.1 and 41.9. Differences in food intake between experimental groups preclude assessment of ureolytic effects on growth. However, ammonium citrate added to complete diets did depress efficiency of food conversion to growth.

ANATOMIC EFFECTS OF NIALAMIDE, A NEW ANTIDEPRESSANT. Robert B. Stebbins and Mary I. Mulroy (Intr. by W. B. Deichmann). Dept. of Macrobiology, Pfizer Therapeutic Institute, Maywood, New Jersey.

Nialamide (NIAMID™), 1-[2-(benzylcarbamyl)ethyl]-2-isonicotinoyl hydrazine, is a potent antidepressant agent with monoamine oxidase (MAO) inhibitor activity. In 150 rats, oral doses of 3 to 30 mg/kg daily for 3 to 6 months caused no gross or microscopic tissue damage. In 23 dogs, levels of 1 to 60 mg/kg daily for 3 to 6 months were likewise innocuous. High levels of 70 to 100 mg/kg were toxic and lethal in a number of dogs after 3 to 15 doses. In practically all these animals respiratory infections were observed grossly and microscopically. In none of these tissues was there found evidence of cellular damage which might be associated with the administration of nialamide. Monkeys receiving oral levels of 10 to 50 mg/kg daily for 1 to 6 months showed no gross or microscopic alterations. A discussion of comparable studies with other MAO inhibitors will be presented.

TOXICOLOGIC STUDIES OF INFUSED UREA IN THE NORMAL DOG. P. J. Garvin*, R. B. Jennings*, and R. M. Gesler. Baxter Laboratories, Inc., Morton Grove, Illinois.

Acute and cumulative toxicologic studies of infused hypertonic urea solutions were carried out in normal dogs. Urea dissolved in 10% invert sugar was infused daily at a rate of 1 ml/min for 7 days into 2 groups of 2 dogs each at doses of 6 g/kg (45% solution) and 8 g/kg (30% solution). Venous and arterial blood samples were taken for blood chemistry initially and on selected days before and after daily infusion. Except for slight weakness observed irregularly, these doses were well tolerated. Food consumption and body weight decreased slightly in all dogs. Daily water intake and urine output increased 3-4 fold. No significant changes were observed in hematology, urinalysis, or histology, or in plasma NH_3, Na, K, or Cl. Plasma urea N was elevated (from av. 20 to av. 395 mg%) immediately after infusion, but became normal within 24 hrs. Another group of 3 dogs given single infusions of 10 and 12 g/kg of urea died within 48 hrs. The post-infusion PUN determined in one dog receiving the 10 g/kg dose was 675 mg% and plasma NH_3 was also increased. The subacute effects of 1 and 2 g/kg of urea (30% solution) infused 5 days/week were studied for 5 weeks in 2 groups of 4 dogs each; no toxicity was observed. These results indicate that repeated infusions of hypertonic urea solutions at daily doses as high as 8 g/kg are well tolerated by dogs with normal renal function. Under these conditions urea is rapidly eliminated, since no accumulation was observed.

CUMULATIVE TOXIC EFFECTS OF REPEATED DOSES OF INHALED GB (SARIN) VAPOR IN DOGS. Fred W. Oberst and Paul Cresthull*. U. S. Army Chemical Warfare Labs, Army Chemical Center, Md.

The cumulative toxic effects from repeated administrations of GB were studied in dogs receiving the vapor dosimetrically by inhalation 2 minutes each day for 5 exposures or every other day for 6 exposures. Dogs were treated with atropine and artificial respiration when needed to maintain life. Doses of 10 to 13 mmg/kg every other day caused only mild signs (cough and slight incoordination) and a fall of RBC-ChE activity to 0% after 5 exposures. Repeated daily doses of 20 mmg/kg caused only moderate signs (tremors, dyspnea, and salivation) and, after the 2nd exposure, 0% RBC-ChE activity. Doses of 23 to 28 mmg/kg caused either mild or moderate signs and 0% RBC-ChE activity after the first exposure and convulsions, collapse, or death after the second. As exposures continued some dogs receiving the vapor every other day showed signs of lesser severity, while dogs exposed daily continued to show severe signs which weakened their physical condition. Severe toxic signs did not occur until the RBC-ChE level approached 0% activity. However, this activity did not always cause severe signs. In some instances no visible signs were seen. The recovery rate for RBC-ChE activity over an 11-day period averaged 1.5% per day. It is concluded that dogs exposed daily to near-lethal doses of GB vapor are more severely affected than those exposed every other day to similar doses.

TOXICITY OF 3-PIPERIDINO-1-PHENYL-1-BICYCLO-HEPTENYLPROPANOL-(1), AKINETON. Calvin Hanna. Dept. of Pharmacology, Univ. of Vt. Med. School, Burlington, Vt.

Akineton is an antinicotinic agent used in Germany as an antitremor agent in the treatment of Parkinsonism. The acute oral toxicity of the drug in the rat and dog expressed as an LD_{50} value is 750 and 340 mg/kg, respectively. A very slight stimulation of the CNS is seen at first, followed by a slight depression with death occurring in 12 to 24 hours. Range finding experiments (35 days) in albino rats indicated that a daily intake of up to 950 mg/kg/day of Akineton in the food could be tolerated. Subacute experiments in dogs (6 mos.) and rats (9 mos.) were carried out. Dogs tolerated 6, 20 and 63 mg/kg/day of the drug but did not tolerate the 200 mg dosage. At the large dose level the dogs lost weight and died over a period of 3 months. The rats tolerated 30, 95 and 300 mg/kg/day in the food but with a retardation of growth on the highest dosage level. Biochemical and hematological analyses of the blood and analyses of the urine of these animals showed no deviation from the normal range. Gross and microscopic examination of organs and tissues of these animals showed no pathological changes attributable to the treatment with Akineton. Grant-in-Aid from Knoll Pharmaceutical Co.

THE EFFECTS OF AGRANULOCYTOSIS-PRODUCING AND OTHER DRUGS IN RABBITS CONCURRENTLY TREATED WITH BUSULFAN. III. MORPHINE, PENICILLIN AND THIOURACIL. F.C. Lu, W.A. Mannell*, H.C. Grice* and M.G. Allmark*. Food and Drug Labs., Dept. of National Health and Welfare, Ottawa, Canada.

It has been found in earlier studies that the granulocyte-depressant action of aminopyrine and chloramphenicol could be demonstrated in rabbits concurrently treated with busulfan but not in rabbits given these drugs alone (Canad. Services Med. J. 12: 513, 1956; Antibiotics Ann. 376, 1956-1957). Further experiments were carried out to ascertain the effects of another agranulocytosis-producing drug (thiouracil) and two other drugs which are not generally considered to cause agranulocytosis. Concurrent treatment of rabbits with thiouracil and busulfan induced a greater drop in the blood granulocyte count than did busulfan alone. The number of granulocytes in the bone marrow was also reduced to a greater extent. Moreover, the ribonucleic acid/desoxyribonucleic acid ratio in these rabbits was considerably higher, indicating an increase in the percentage of premature cells. Finally, thiouracil when given alone had no effect on the blood cell count and appeared to stimulate the bone marrow slightly. These findings indicate that thiouracil is similar to aminopyrine and chloramphenicol in hematological effects. On the other hand, morphine and penicillin, when tested in a similar manner, yielded negative results.

SOME PHARMACOLOGICAL PROPERTIES OF SELECTED ANTIBIOTICS. Floyd Leaders*, J. P. Long and C. B. Pittinger. Dept. of Pharmacology, College of Medicine, State University of Iowa, Iowa City, Iowa.

The clinical observation of hypotension following I.P. administration of streptomycin at the termination of abdominal surgery prompted this study. The antibiotics streptomycin sulfate, dihydrostreptomycin sulfate, chloramphenicol succinate, tetracycline hydrochloride and oleandomycin phosphate were administered to rabbits by I.V. infusion. Blood pressure was lowered in all cases. Heart rates were slowed from 16% to 58%. Heart blocks and other arrhythmias were frequently observed. Isolated rabbit ileum preparations showed reversible antagonism to acetylcholine in all cases studied. Similarly, histamine antagonism was observed with all antibiotics but oleandomycin. Langendorff isolated rabbit heart preparations were utilized to study myocardial effects of these drugs and results of these studies will be discussed.

INHIBITION OF CARBONIC ANHYDRASE BY CHLORINATED INSECTICIDES. Mary J. Verrett and Alton H. Desmond (intr. by Edwin P. Laug). Div. of Pharmacology, Food and Drug Adm., Washington, D. C.

Three groups of chlorinated insecticides were tested for their inhibitory effect on crude Carbonic Anhydrase: (A) DDT, DDD, DDE (dehydrochlorination product of DDT), and Methoxychlor; (B) Aldrin, Dieldrin, and Endrin; (C) alpha-, beta-, and gamma- hexachlorocyclohexane. At enzyme dilutions of 1:85,000, 1:42,500, 1:21,250, and 1:10,625, and an inhibitor concentration of 5.9×10^{-4}M, group (A) caused inhibition of 90-100%, group (B) 75-85%, and group (C) 1-15% (gamma-isomer only, the alpha- and beta-isomers were negative throughout). An inhibitor concentration of 2.9×10^{-5}M gave 1-20% inhibition with group (A) and 0-5% with group (B). Due to the insolubility of the compounds, the active inhibitor concentration may be somewhat less than that stated. Active concentration of the inhibitor is being investigated by other means. The inhibition was determined in Warburg vessels at 5°C with Carbonic Anhydrase from rat blood diluted in phosphate buffer (0.1M, pH 6.9), stabilized by the addition of 0.05% peptone; $NaHCO_3$ (0.1M); and the inhibitor (98% pure or better) dissolved in 95% ethanol. The effect of varying substrate concentration on the inhibition of DDT, at a DDT concentration of 4.4×10^{-4}M, indicates a mixed inhibition.

THE EFFECT OF ADRENERGIC BLOCKADE, ADRENALECTOMY AND CORD SECTION ON RAT LIVER PATHOLOGY PRODUCED BY CCl_4. Deane N. Calvert*, Theodore M. Brody and Albert F. Schneider† Depts. of Pharmacology and Pathology, Univ. of Michigan Med. School, Ann Arbor.

Excellent correlation was observed between biochemical function of mitochondria, lipid analyses and histopathological findings following a single oral hepatotoxic dose of CCl_4. Simultaneous administration of the adrenergic blocking agents and CCl_4 resulted in protection against the centrilobular necrosis and a diminution of the fatty infiltration usually observed with CCl_4 alone. Adrenalectomy performed prior to CCl_4 administration resulted in some protection against centrilobular damage and no fatty infiltration was seen. Transection of the spinal cord at the level of T-1 afforded complete protection; the livers were indistinguishable grossly, biochemically or histologically from untreated, operated controls. The histological findings will be discussed in the light of our hypothesis (Calvert and Brody, Fed. Proc. 18, 375, 1959) that the mechanism of hepatotoxicity of CCl_4 is an indirect one, the primary event being mediated through stimulation of the sympathetic nervous system. The centrilobular necrosis and fatty infiltration are separable events although both phenomena may be attributable to the liberation of catechol amines.

Supported by USPHS RG-4759 C2.

NERVE AND MUSCLE
Room N-205, Memorial Building

ANALYSIS OF THE BLOCKING ACTION OF VERATRINE ON NERVE CONDUCTION. Alaeddin Akcasu* and Ferenc Herr. Dept. of Pharmacology, Univ. of Illinois Coll. of Medicine, Chicago, Ill.

The blockade of nerve conduction by veratrine can be eliminated by anodal polarization and some local anesthetics. Experiments were performed on desheathed sciatic nerves of the frog with regard to the blocking action of veratrine and its reversal by different procedures. Square wave pulses were employed to stimulate the nerves and cathode ray oscilloscope recordings of the conducted compound action potentials were made before and after immersing the whole nerve into the solutions under investigation. 10 μg/ml of veratrine blocked conduction in one minute. Changing to Ringer solution restored conduction if this change was made within 3 min. after the onset of the blockade. However, the return of nerve conduction was transient and within 60-120 min. the blockade reappeared. In concentration of 2 μg/ml, veratrine blocked nerve conduction in about 60-120 min. and this blockade was irreversible. Procaine (100 μg/ml) antagonized the blockade produced by 10-100 μg/ml of veratrine but not the blockade produced by 2 μg/ml. Ca and Mg ions also restored nerve conduction after veratrine blockade in a similar manner as local anesthetics. It is suggested that there are two mechanisms underlaying the blocking action of veratrine; only the blockade produced by large concentrations of veratrine can be antagonized. (Supported in part by Grant B-973, USPH.)

VERATRINE RESPONSE AND ANTIVERATRINIC ACTIVITY. W. Flacke (intr. by O. Krayer). Dept. of Pharmacology, Harvard Medical School, Boston, Mass.

Veratramine, quinine, ouabain, erythrophleine, cocaine, increased concentration of calcium and of potassium and decrease of sodium in the medium antagonize the aftercontraction produced by veratridine in skeletal muscle without affecting the twitch. However, in frog sartorius muscles stimulated directly with supramaximal shocks all agents listed except calcium reduced tension developed during tetanic stimulation. Thus calcium possesses a higher degree of antiveratrinic specificity than all other agents. Nevertheless, even calcium did not restore the muscles to the condition before addition of the alkaloid: Relaxation of the muscle after tetanic stimulation in the presence of veratridine was slow even when the aftercontraction following a twitch had been completely abolished by a high calcium concentration. (Supported by USPHS Grant H-2205.)

A CHARACTERIZATION OF THE SUCCINYLCHOLINE INDUCED STIMULATION OF MAMMALIAN MUSCLE SPINDLES. John C. Brinling* and Cedric M. Smith. Dept. of Pharmacology, Univ. of Illinois Coll. of Medicine, Chicago, Ill.

The rapid intravenous administration of succinylcholine (SCh) produces a marked, transitory stimulation of the stretch receptors in muscle spindles (Granit, R. et al: Acta Physiol. Scand. 28: 134-151, 1953). The excitation of the stretch receptors of the gastrocnemius muscle of the cat by SCh was investigated, recording oscillographically the action potentials of functionally single fibers isolated in dorsal root filaments. The responses to the repeated intravenous administration of a given dose of SCh (100, 200 or 400 ug/kg) showed no evidence of tachyphylaxis or cumulation provided a sufficient time interval (15-30 min) elapsed between injections. A skewed sigmoid log dose-response curve was obtained with doses ranging from 12.5 to 600 ug/kg. Continuous infusions of SCh (200-1600 ug/kg/min) produced a marked acceleration of the spindle discharge which continued unabated as long as the infusion was maintained. These results are consistent with the assumption that SCh acts primarily at the neuromuscular junctions of the intrafusal muscle fibers. (Supported in part by Grant B-973, USPH.)

DOSE METAMETERS FOR NEUROMUSCULAR BLOCKING AGENTS. Edward J. Pelikan. Dept. of Pharmacology and Experimental Therapeutics, Boston Univ. School of Medicine, Boston, Mass.

A significantly linear relation exists between log mean total paralyzing dose (Hoppe's data) and log mean body weight for various homeotherm species for tubocurarine (I), its dimethyl ether (II), bensoquinonium (III), gallamine (IV), decamethonium (V), and succinylcholine (VI). Slopes of curves for I, II, III, IV and VI did not differ significantly from each other or from 1.0; the slope for V was less than 1.0 and differed from those of I and VI. Standard error of estimate was greatest for V, least for I. Apparent species differences in sensitivity existed only when dose was expressed in mg/kg for all species and drugs. Potency of V was incommeasurate with those of I, II, III, IV or VI except in species of identical weight. For individual normal men log total dose of I to decrease grip strength 95% was linearly related to log body weight, the slope did not differ from 1.0; no such relationship existed for V. Potencies of V and I were incommeasurate except in men of identical weights. In normal men, log total dose of V or I to just affect extraocular muscles was linearly related to log body weight; potencies of V, but not I, on different muscle groups in men were incommeasurate except in individual subjects. For these drugs, estimations of potency, description of species or subject variation, and identification of variant species and drugs to which variation occurs, depends on the method chosen to express dose.

A COMPARATIVE STUDY OF RYANODINE SENSITIVITY. Wilford L. Haslett* and Donald J. Jenden. Dept. of Pharmacology, UCLA Medical Center, Los Angeles 24, California.

Ryanodine, an alkaloid obtained from plants of the genus Ryania, is known to produce rigor in vertebrate striated muscle. A phylogenetic survey of sensitivity to ryanodine has been conducted in an attempt to throw some light on its mechanism of action by correlating the results with known biochemical, physiological and morphological characteristics of muscle from each species. Isolated muscle strips were used wherever possible to test sensitivity; tetanic electrical stimulation was applied at regular intervals in order to confirm the viability of the preparations. In more than 25 species examined it has not been possible to correlate the occurrence of any particular phosphagen with the effects of the drug. With the exception of vertebrate intestine, all smooth muscle studied appears to be insensitive to ryanodine while cross-striated muscle is sensitive. In the light of evidence to be presented it seems likely that sensitivity to this compound is largely determined by the degree of morphological specialization of the muscle cell, and that the action of Ryania may be exerted primarily on intracellular coordination mechanisms.

DERIVATIVES OF 3-PYRROLIDINOLS-II. Arthur Pallotta, John Ward, Carl Lunsford, Richard Mays, and Robert Murphey. (intr. by L.W. Hazleton). Research Laboratory, A. H. Robins, Co., Inc., Richmond, Va. and Hazleton Laboratories, Inc., Falls Church, Va.

The chemistry, pharmacology and toxicology of a series of N-substituted-3-pyrrolidyl-substituted benzoates were investigated for local anesthetic activity. A series of N-substituted 3-pyrrolidinols have been prepared by the condensation of primary amines with 1,4-dibromo-2 butanol. The present paper reports the synthesis of a series of benzoates and substituted benzoates of this 3-pyrrolidyl system. The in vitro local anesthetic activity as determined by the electrophysiological technique and in vivo local anesthetic activity as determined by the guinea pig wheal, corneal, nerve block and spinal anesthesia were investigated. In addition, acute toxicity, peripheral vascular activity and local irritative potential were also investigated. As a result of these studies, several of the N-substituted-3-pyrrolidyl substituted benzoates have been shown to be effective local anesthetics. The weight of the N-substituent significantly influenced anesthetic activity. Further structural activity relationship will be discussed.

LOSS OF RED CELL POTASSIUM INDUCED BY BARBITURATES. G.H. Acheson and G. Grupp*. Dept. of Pharmacology, Univ. of Cincinnati College of Medicine.

Pentobarbital (2 to 40 mEq per L. of blood) causes human red cells to lose potassium to the surrounding plasma or saline. The rate of loss accelerates during the first hour and is then steady until a maximum when plasma potassium approaches whole blood potassium. The rate of loss rises sharply with concentration of barbiturate and may reach 70 mEq per L. of cells per hour. With rapid loss, the cells swell and hemolyze some time after the maximum loss has been reached. Ten barbiturates gave similar effects, with a tenfold range of potency, the long-acting ones and vinbarbital being 3 to 6 times less potent and methitural being about 3 times more potent than pentobarbital.

FACTORS INFLUENCING RED CELL POTASSIUM LOSS PRODUCED BY PENTOBARBITAL. G. Grupp* and G.H. Acheson. Dept. of Pharmacology, Univ. of Cincinnati College of Medicine.

The potassium loss of human red cells produced by pentobarbital at 37°C is decreased at 23°, but at 0° it is almost as large as at 37°C. In contrast, the loss produced by ouabain is less at 23° and practically absent at 0°. When sufficient concentrations of both compounds are present, the pentobarbital action predominates.

When plasma potassium is raised (20 to 100 mEq per L.) pentobarbital in concentrations above 4 mEq per L. of blood produces a decrease of plasma potassium for about 30 min., followed by an increase. Lowering the temperature to 23° increases and prolongs the early fall of plasma potassium. Ouabain does not show these effects. The rate of potassium loss produced by pentobarbital decreases with increasing plasma potassium, approaching zero at about 100 mEq of potassium per L. of plasma.

Red cells which have lost potassium as a result of exposure to high pentobarbital concentrations regain potassium from the supernatant after they have been washed. Cells cold-stored for 24 hours lose potassium; the regaining of potassium which occurs on rewarming to 37° is decreased by pentobarbital.

POSSIBLE ROLE OF SEROTONIN IN RESERPINE-INDUCED RELEASE OF HISTAMINE FROM RABBIT BLOOD. A. Burkhalter*, and P.A. Shore. National Heart Institute, Bethesda, Md.

It has been demonstrated that reserpine administration to rabbits lowers histamine as well as serotonin levels in blood. Since a Rauwolfia alkaloid (methyl reserpate) which is inactive in releasing serotonin from rabbit blood did not release histamine, and since serotonin has been shown capable of releasing histamine from mast cells, we have investigated the ability of serotonin to release rabbit blood histamine. Intravenous infusion of serotonin (4-8 μg/kg/min.) or administration of the serotonin precursor, 5-hydroxytryptophan, results in a lowering of histamine concentration in rabbit whole blood and in platelets. These findings are consistent with the possibility that reserpine-induced release of histamine from rabbit blood is mediated by the released serotonin.

EVIDENCE FOR BOTH RELEASE AND PROTECTION OF BRAIN NOREPINEPHRINE AND SEROTONIN IN VIVO AFTER GIVING RESERPINE IN PRESENCE OF MONOAMINE OXIDASE (MAO) INHIBITORS. S. Spector*, R. Kuntzman*, P.A. Shore and B.B. Brodie. National Heart Institute, Bethesda, Md.

Administration of reserpine to rabbits after giving iproniazid blocks the sedative action and the decrease in brain amines. This has been interpreted as a blockade of the actual release process despite LSD-like effects elicited by the drug combination. However, if reserpine is given after harmaline, a reversible MAO inhibitor, sedation and the fall in brain amines are blocked for a short time only. As effects on MAO decrease, amine levels fall and sedation occurs. This supports the thesis that reserpine actually releases the amines which are protected in free form by action of MAO inhibitors. Further evidence is obtained when harmaline, iproniazid and reserpine are given in that order. Harmaline blocks the prolonged action of iproniazid on MAO; as a result, sedation and fall in brain amines are soon obtained. These results show the predominant role of MAO in metabolism of brain norepinephrine.

INHIBITION OF RESERPINE TRANQUILIZING EFFECTS BY STRESS. Fridolin Sulser*, Kenneth F. Finger* and B.B. Brodie, National Heart Institute, Bethesda, Md.

Reserpine causes a simultaneous release of brain norepinephrine and serotonin in normal rats and rabbits. In stressed animals (exposure to cold, intradermal formaldehyde, parenteral methylcholanthrene) reserpine has little or no effect on brain serotonin, but depletes brain norepinephrine. These animals show no depression or other central effects. Thus the tranquilizing action of reserpine seems to be related to the release of brain serotonin rather than to norepinephrine depletion. In hypophysectomized rats, stress does not block sedation or serotonin depletion following reserpine. Stress has no effect on chlorpromazine induced sedation.

RELATIONSHIP BETWEEN TRANQUILIZING EFFECTS OF VARIOUS BENZOQUINOLIZINE DERIVATIVES AND LEVELS OF BRAIN HT. Gertrude P. Quinn and Bernard B. Brodie. National Heart Inst., Bethesda, Md.

Recent studies of Pletscher et al. with two benzoquinolizine tranquilizing agents suggested that the sedative effects of Ro 4-1284 and Ro 4-1398 in mice were related to the release of brain NE rather than HT. This conclusion was based on findings one hour after drug administration at which time both compounds were equally effective in releasing HT but Ro 4-1284, the more potent tranquilizer, had released more NE. Our studies on the time course of the drug release of brain amines demonstrate that brain HT and NE are released extremely rapidly, minimum levels occurring in about 30 minutes, and that Ro 4-1284 releases considerably more HT than Ro 4-1398. Brain HT levels then rise rapidly while the levels of NE rise slowly because of its slower rate of biosynthesis. Thus in one hour the HT brain levels have already been restored to a considerable extent and measurements taken at this time only, would make it appear that the release of HT was not important in the action of these drugs. Our data suggest that the differences in the degree of sedation observed with these compounds may be attributed to changes in brain HT.

AN EFFECT OF MONOAMINE OXIDASE INHIBITORS ON BRAIN SEROTONIN POSSIBLY IN ADDITION TO THAT RESULTING FROM INHIBITION OF MONOAMINE OXIDASE. Bernard Dubnick, Gerald A. Leeson and George E. Phillips, (intr. by C. C. Scott). Warner-Lambert Res. Inst., Morris Plains, N. J.

It has been shown that serotonin levels in mouse brain increase to a degree dependent upon the dose of β-phenylethylhydrazine (I), an "irreversible" inhibitor of monoamine oxidase (MAO). Although it was reasonable that the levels of serotonin should be related to the degree of MAO inhibition, those levels continue to increase with doses of I which exceed the dose required for complete inhibition of MAO, as measured by serotonin disappearance in mouse brain homogenates. Furthermore, during 24 hours the serotonin levels recede from the peak levels induced by an excessive dose of I (> 16 mg/kg, i.p.), although MAO apparently remains completely inhibited. A "booster" dose of some MAO inhibitors (e.g., β-phenylethylhydrazine, phenylisopropylhydrazine and harmaline) causes serotonin levels to rise again, when given 24 hours after the initial dose of I; some non-inhibitors (e.g., isoniazid and hydrazine) do not. The "booster" portion of the serotonin increase will be characterized by comparison with the rise after a single dose of I, with respect to such parameters as rate of serotonin accumulation, response to MAO inhibitors of varying potency and reversibility.

PHENYLETHYLAMINE AND ORTHO-TYRAMINE FORMATION IN PHENYLKETONURIA. J.B. Jepson*, W. Lovenberg*, A. Sjoerdsma, J. Oates*, P. Zaltzman*, and S. Udenfriend. National Heart Institute, Bethesda, Md.

Administration to patients of monoamine oxidase inhibitors (MAO-I) serves to uncover hitherto unsuspected pathways of amine formation. Hypertensive, but otherwise normal, patients on MAO-I therapy (JB-516, 25 mg/day) excrete ortho-tyramine in the urine (approx. 50 μg/day). In phenylketonuria there is a large urinary excretion of ortho-hydroxy-phenylacetic acid and phenylacetic acid, but no detectable ortho-tyramine or phenylethylamine; however, ortho-tyramine and phenylethylamine appeared in mg. quantities in a phenylketonuric on the MAO-I regimen, though the excretion of acids was not markedly diminished. By contrast, phenylethylamine was barely detectable in MAO-blocked non-phenylketonurics, even when heavily dosed with phenylalanine. Phenylethylamine and ortho-tyramine are the first compounds with known physiological action whose accumulation is greater in phenylketonurics than in normals; their relation to the hydroxylation defect will be discussed.

INTRACELLULAR DISTRIBUTION OF NORADRENALINE IN RAT BRAIN. Harry Green, John Sawyer, and Robt. Erickson. (Intr. by L. Cook) Research & Development Division, Smith Kline & French Laboratories, Philadelphia 1, Pa.

Homogenates (1:2) of rat brains prepared in 0.3M sucrose were centrifuged at 100,000 g. for 30 min. The residue (R), after washing 2x with sucrose, contained the stored noradrenaline (NAd), while the high speed supernatant (S) contained the free NAd. The average R/S ratio of NAd conc. was 1.158, with quantitative recovery of the NAd present in the homogenate. With the monoamine oxidase (MAO) inhibitors, Marsilid and 2-phenylcyclopropylamine (SKF 385), under conditions in which the NAd conc. increased 50% and 85%, resp. (Marsilid, 40 mg/kg, p.o., 8 hr.; SKF 385, 5 mg/kg, p.o., 5 hr.), the distribution of NAd between R and S was substantially the same as that of the controls. Reserpine (5 mg/kg, i.p.) caused a marked release of the stored NAd into the sol. cytoplasm within 15 min., followed by a progressive decline of the conc. in the latter. Depletion of NAd was complete in 60-90 min. SKF 385 administered 60 min. after Reserpine had no appreciable effect upon the NAd conc. for 5 hr. Prior administration of SKF 385 prevented the depletion of NAd by Reserpine at least for 2 hr. The SKF 385-induced increase of NAd conc. was erased by Reserpine, without any appreciable effect upon the distribution of the remaining normal level of NAd between R and S. The implications of these results relative to the mode of action of MAO inhibitors and of Reserpine will be discussed.

INCREASED BEHAVIORAL EFFECTS OF 5-HYDROXYTRYPTOPHAN BY IPRONIAZID PRETREATMENT. C. B. Ferster and M. H. Aprison (Introduced by K. K. Chen) Indiana University Medical Center, Indianapolis, Ind.

A dose-effect relation was determined between intramuscularly injected 5-HTP and the pecking response of a pigeon in an experimental chamber under a multiple fixed-interval, fixed-ratio schedule of reinforcement. Injections of 8-75 mg/kg of 5-HTP produced corresponding disruptions of the pigeon's performance. The behavioral change ranged from a slight decline in rate at the lower doses to a complete cessation of pecking at the higher doses. The duration of the effect increased with dose and the baseline performance was recovered before the bird completed the experimental session (5-8 hrs.) The birds remained standing throughout. The same pigeons, given three 50 mg. injections (IM) of iproniazid on three successive days, showed no behavioral effect of the injected drug. Injections of 5-HTP 1.5 hrs. after the third iproniazid injection produced a greater effect than the original dose. The enhanced effect of injections of the same dose of 5-HTP in the same bird over a period of several weeks declined with time after the iproniazid pretreatment. The rate of return to a pre-iproniazid level depended on the 5-HTP dose. The nature of the behavioral curve was similar to curves expressing brain monoamine oxidase activity after iproniazid pretreatment.

THE EFFECT OF ACUTE AND CHRONIC ADMINISTRATION OF ETHYL ALCOHOL ON THE EEG AND AVOIDANCE BEHAVIOR OF CHRONIC ELECTRODE MONKEYS. Alice F. Hogans,* David A. Brodie, Oscar M. Moreno* and Elliott A. Meltzer.* Merck Institute for Therapeutic Research, West Point, Pa.

The electroencephalogram and avoidance behavior of monkeys with chronically implanted cortical electrodes, trained on a modified Sidman avoidance schedule, were studied following acute and chronic administration of ethyl alcohol. Blood alcohol levels were measured before alcohol administration and at several fixed times after the intravenous injection. Acute administration of alcohol in doses of 0.5 to 2.0 gm./kg. produced blood alcohol levels in the range of 50 to 250 mg.%. As the blood alcohol level was raised, the impairment of avoidance responding was correlated with an increase in signs of CNS depression. A dose of 2.0 gm./kg. of alcohol was administered I.V. once daily until signs of behavioral deficit were minimal. Initially, avoidance behavior was abolished and spontaneous EEG activity was markedly slowed for a period of 30 minutes after the alcohol injection. When tolerance to the behavioral effects of alcohol occurred, the EEG still showed high voltage, slow wave activity. This study suggests that tolerance to the behavioral effects of ethyl alcohol may be acquired independently of central nervous system tolerance as measured by cortical EEG activity.

AN EEG STUDY OF PSYCHOTROPIC DRUGS IN ANIMALS. Donald F. Bogdanski, Guy C. Sheatz*, and Robert Galambos*. Dept. Otolaryng., Univ. of Maryland Med. School, Baltimore, Md., and Dept. Neurophysiol., Walter Reed Army Inst.of Rsch.,Wash.,D.C.

EEG studies in normal cats and monkeys with chronic implantation of cortical and subcortical electrodes have shown that responses evoked by click stimuli in auditory and non-auditory areas increase in amplitude and complexity when the conditioning stimulus (CS) is reinforced by an unconditioned stimulus such as air puff or electric shock. Preliminary tests show that the psychotomimetic drug lysergic acid diethylamide (LSD, 10 microgrm./kgm.), and the serotonin precursor 5 hydroxytryptophan (5-HTP, 10 mgm./kgm.) increase the unconditioned response to CS, and more strikingly, the extinguishing response. d-Amphetamine sulfate (2 mgm./kgm.) an adrenergic drug, produces a smaller, equivocal increase. A large response to the CS is diminished or abolished by pentobarbital (3 mgm./kgm.), chlorpromazine hydrochloride (1 mgm./kgm.) and the cholinergic drug physostigmine sulfate (2 mgm./kgm., i.m.). Thus various classes of drugs influence the neural events underlying the EEG phenomenon in different ways. It is interesting to note that although adrenergic and cholinergic mechanisms have been postulated in the reticular formation of the brain, examples of each class produce different effects on the response to CS. Moreover, they differ from both 5-HTP and LSD, suggesting that different mechanisms are involved.

CARDIOVASCULAR PHARMACOLOGY V

Room N-202, Memorial Building

THE NATURE OF CARDIAC ARRHYTHMIAS INDUCED BY MINIMAL DOSES OF EPINEPHRINE IN CYCLOPROPANE-ANESTHETIZED DOGS, by Peter E. Dresel, Dept. of Pharmacology and Therapeutics, Faculty of Medicine, University of Manitoba, Winnipeg, Canada.

The chests of dogs anesthetized with thiopental were opened and stimulating and recording electrodes attached to the right atria. 20% cyclopropane in oxygen was then administered. Epinephrine was given in doses of 0.25-4.0 µg/Kg over 50-60 seconds. Lead II EKG, atrial electrograms and blood pressures were recorded simultaneously. The electrocardiographic changes due to the minimal doses were not necessarily consistent with the commonly accepted hypothesis of the emergence of a ventricular focus of increased automaticity. They included atrioventricular nodal block, coupled beats, bigeminal rhythm at a total rate usually equal to the atrial rate, accompanied by a pulse deficit. Obvious focal ventricular tachycardias were not seen until larger doses of epinephrine were infused. Vagotomy had no effect on the threshold dose for these electrocardiographic abnormalities. At threshold doses the abnormalities usually started close to, or after completion of the infusion. The pulse deficit can be shown to disappear when bigeminal rhythm is changed to ventricular tachycardia. The hypothesis that the changes observed are due to myocardial depression, especially of the ventricular conduction system, will be considered in detail.

A PROCEDURE UTILIZING UNANESTHETIZED MICE FOR DETERMINING THE POTENTIAL OF NEW COMPOUNDS AS VENTRICULAR ANTIFIBRILLATORY AGENTS. James W. Lawson† and Elizabeth R. Rahdert (intr. by Benedict E. Abreu). Research Center, Pitman-Moore Co., Indianapolis, Ind.

The mouse heart is immediately exposed and observed for ventricular fibrillation following respiratory arrest produced by chloroform inhalation. In twelve parallel control groups (ten mice each) 90% developed either continuous or intermittent ventricular fibrillation. Procaine amide protects against the development of this ventricular fibrillation, its peak activity time (i.p.) being approximately ten minutes. A procaine amide dose-response curve was plotted and the ED_{50} was calculated to be 150 mg./kg. This method also affords a means for establishing the dosage range between antifibrillatory activity and untoward effects. Visual observations were confirmed by photographing electrocardiograms (Lead II) obtained on a cathode ray oscilloscope.

†Now at Alcon Laboratories, Fort Worth, Texas

EFFECTS OF DICHLOROISOPROTERENOL ON CARDIAC CONDUCTION AND REFRACTORY PERIODS. Joanne I. Moore and Benedict R. Lucchesi (Intr. by H.H. Swain), Univ. of Michigan, Ann Arbor.

Certain cardiac actions of dichloroisoproterenol (DCI, Lilly Compound 20522) were measured in the dog heart-lung preparation. Small doses up to 10 mg speed intracardiac conduction while larger doses up to 50 mg slow conduction. The actions are most prominent upon A-V conduction, less striking on auricle-to-auricle conduction, and minimal upon conduction within the ventricle. The refractory periods of auricle and ventricle are usually shortened slightly by the small doses of DCI and always prolonged by the large doses. These actions of DCI on conduction and refractory period are not mediated through nor-epinephrine release, because these actions are not prevented by reserpine pretreatment of the subject dogs or by cocaine blockade. The small doses of DCI employed are sufficient to block the conduction and refractory period effects of infused epinephrine (10 ug/min). The ability of DCI to prevent certain epinephrine-induced cardiac arrhythmias (Moore and Swain, Fed. Proc. 17: 396, 1958; Moran and Perkins, J. Pharmacol. 124: 223, 1958) appears to be due to receptor blockade and not to the direct actions of DCI upon cardiac conduction and refractory periods.

(Supported by PHS Grant H-2466-C2.)

THE ROLE OF ELECTROLYTES ON THE ANTIVERATRINIC ACTION OF ANTIARRHYTHMIC DRUGS. R. B. Arora (intr. by Arthur Grollman). Dept. of Pharmacology, All-India Inst. of Medical Sciences, New Delhi 16, India.

Veratridine produces an efflux of K^+ from skeletal muscle. Although K^+ per se has antiveratrinic and antiarrhythmic action, the rise of serum K^+ concentration in arrhythmias is nonspecific. However, a specific increase in magnesium concentration of coronary sinus blood was observed in atrial fibrillation induced by Aconitine and acetylcholine but not in "injury-stimulation" flutter. This finding stresses the importance of the circus wave theory of flutter. Though all auricular antiarrhythmics possess antiveratrinic action, this can not be correlated on the basis of their chemical action or the efflux of K^+ and/or Mg^{++} from skeletal and cardiac muscle.

ROLE OF STIMULATION RATE ON THE QUINIDINE EFFECT ON DEPOLARIZATION AND REPOLARIZATION IN RABBIT ATRIUM. Theodore C. West and David W. Amory* Dept. of Pharmacology, Univ. of Washington School of Med., Seattle, Wash.

Transmembrane potentials in rabbit isolated right atrium deprived of normal pacemaker tissue were recorded by the microelectrode technique. Contraction force was measured by means of a strain gauge. The preparation was driven at any desired rate by electrical stimulation. The basal rate was 2/sec. Oxygenated Ringers solution containing 5.4 mM/L of KCl was used. The bath temperature was 37° C. Recordings were made on a dual beam oscilloscope and were analyzed for the maximum rate of membrane depolarization and for the time required for repolarization at three levels: 10%, 50% and 90%. After establishing controls, quinidine sulfate, 6 mgm/L in Ringers solution, was perfused through the bath. Within one hour repolarization time at each of the three levels was prolonged at all rates of stimulation from the maximal follow rate to 0.1/sec. Depolarization rate was greatly reduced at frequencies near the maximum follow rate but was essentially unchanged at low stimulation rates. It is concluded that the known effect of quinidine on depolarization rate is closely related to the rapidity of repolarization, which in turn is a function of heart rate.

QUINIDINE AND CATION PERMEABILITY IN ATRIA. Richard L. Klein* and William C. Holland. Dept. of Pharmacology, University of Mississippi Medical Center, Jackson, Miss.

The effects of quinidine on the unidirectional fluxes of K^{42} as influenced by temperature and extracellular concentrations of Na and K were studied in isolated rabbit atria. Quinidine has an immediate effect to depress K efflux, which has been shown by net Na^{24} uptake studies to be secondary to an inhibition of Na entry. This effect can be reversed by raising $(Na)_o$, by high voltage stimulation, and in media with low $(K)_o$ and low $(Ca)_o$. Quinidine's effect to block Na entry can best be correlated with a decrease in the maximum following frequency and changes in the rate of depolarization and duration of the transmembrane action potential. The more delayed effects of quinidine are a marked depression of active transport of K and Na, and a moderate decrease in membrane permeability to K. The inhibited active transport cannot be reversed by the conditions which reversed the drug's effect to decrease K efflux. The block of active transport can best be correlated with a diminished amplitude of beat, which occurs after a relatively long term exposure to quinidine.

FACTORS AFFECTING Ca^{45} AND Cl^{36} EXCHANGE IN RABBIT ATRIA. W.C. Holland and A.A. Sekul*. Dept. of Pharmacology, Miss. Med. Center, Jackson, Miss.

A number of factors affecting Ca^{45} and Cl^{36} exchange have been investigated. Resting Ca^{45} influx was estimated to be 0.024 pmoles $cm^{-2}sec^{-1}$. Absolute efflux was not determined. Ouabain ($1x10^{-6}M$) almost doubled influx. Increasing calcium concentration in medium (Ca_o) or decreasing the potassium (K_o) enhanced this effect. An increase of K_o blocked the action of ouabain. Acetylcholine (Ach) and quinidine had no effect on calcium exchange. Resting Cl^{36} influx and efflux was estimated to be approximately 1.7 pmoles $cm^{-2}sec^{-1}$. Ouabain increased influx 35% but had no effect on efflux. Ach and quinidine had no effect on Cl^{36} exchange. With onset of fibrillation Ca^{45} influx almost tripled, with rapid stimulation it doubled. The rate of efflux was unchanged. Rapid stimulation increased Cl^{36} influx and efflux by a factor of 2. Fibrillation while increasing efflux to a same degree as stimulation had a much greater effect on Cl^{36} influx. Conclusion: The systolic action of ouabain is probably a result of increased Ca^{45} influx. Its action on active transport could be the result of this effect on calcium exchange. Ouabain also affects passive membrane transport as evidenced from its effect on Cl^{36} transport. Fibrillation results from a marked increase of sodium influx. Increased Cl^{36} influx suggests that the sodium inactivation process is increased during fibrillation.

OBSERVATIONS IN UNANESTHETIZED DOGS ON INTRINSIC RHYTHMICITY OF THE VENTRICLE. Jay Roberts, Michael J. Olichney*, Jean W. Roughgarden* and Walter Modell. Dept. of Pharmacology, Cornell University Medical College, New York, N.Y.

These observations were made in dogs which had completely recovered from an operation causing permanent heart block with a ventricular rate averaging 47. The auricular rate continued at a normal of 160. When these animals were given reserpine (0.1 mg. per Kg., IV) the ventricular rate fell to about 21 within 24 hours while the auricular rate fell to 128. The administration of Eumydrin was without significant effect. Given before reserpine, hexamethonium reduced the ventricular rate to 28, while after reserpine and Eumydrin, it reduced it to 14. In a similar preparation, a ventricular rate of 52 was reduced to 21 by sympathectomy. Since there was progressive slowing of the idioventricular rate by measures which diminish sympathomimetic activity, these observations are suggestive that, in a large part at least, the so-called intrinsic rhythmicity of the ventricle depends on catechol amine content of cardiac tissue and its availability through activity of the sympathetic nervous system.

REFRACTORY PERIOD CHANGES AND VENTRICULAR FIBRILLATION. Henry H. Swain, Univ. of Michigan, Ann Arbor.

If the ventricle of a dog heart-lung preparation is driven electrically at progressively increased frequencies, it will respond to each stimulus up to rates of about 600 beats/min. If the stimuli are 2 times threshold intensity, further increase in driving frequency will be accompanied by an abrupt transition to 2:1 following, where every other stimulus fails to evoke a response. If the stimulus is 3X threshold, the ventricles fibrillate instead of going to a 2:1 rhythm when the driving frequency exceeds that which the ventricles can follow 1:1. Fibrillation can be terminated by 110 V AC countershock. The ventricular refractory period can be prolonged with little change in ventricular conduction with Upjohn compound U-0882 (Moore and Swain, Fed. Proc. 17: 396, 1958). After 10 mg of U-0882 in the HLP, the ventricle will follow frequencies up to 480 beats/min.; higher frequencies cause 2:1 following with 2X threshold stimuli and fibrillation with 3X threshold stimuli. After 30 mg of U-0882 the transition frequency is 390 beats/min. U-0882 does not change the threshold or make fibrillation more difficult to induce, but lowers the driving frequency necessary to initiate the condition. In all instances fibrillation occurs at frequencies where the stimulus is falling in the relative refractory period of the immediately preceding beat.

(Supported by PHS Grant H-2466-C2.)

ANALGESICS

Room N-204, Memorial Building

SOME WITHDRAWAL SYMPTOMS OF RATS TO MORPHINE. Eikichi Hosoya (intr. by L. A. Woods). Dept. of Pharmacology, School of Medicine, KEIO Univ. Yotsuya, Tokyo.

The effect of repeated morphine admin. on body weight (B.W.) was studied in rats injected subcutaneously twice daily, with increasing doses (20 mg/kg to 100 mg/kg) of morphine sulfate. Control animals were injected with physiol. saline solution. The following facts were recognized: (1) If B.W. is less than 100 gm, the increase of B.W. of rats receiving morphine is the same as control rats. (2) If B.W. is in the range of 100-200 gm, the increase of B.W. of rats treated with morphine is less than control animals. (3) If B.W. of the morphine treated rats is over 200 gm, there is little or no increase in B.W. If B.W. exceeds 300 gm initially, B.W. begins to decrease. (4) Substitution of saline solution for morphine in rats receiving morphine for over 4 weeks causes without fail a sharp decrease of B.W. 24 hours after withdrawal. This decrease of B.W. depends chiefly upon the decrease of food and water intake. The B.W. increases 48 or 72 hrs. after withdrawal. (5) At the beginning of the long experiment the movement of rats is depressed severely by morphine injection, then the depression disappears and the movement becomes more active day by day. Abrupt withdrawal of the drug causes a significant depression again. These processes are quantitatively shown by Yanagita's instrument.

QUANTITATIVE EEG STUDIES ON THE ACTION OF MORPHINE AND NALORPHINE, AND ON THE ANTAGONISM BETWEEN THESE TWO SUBSTANCES. Leonide Goldstein and Jorge Aldunate (intr. by Carl C. Pfeiffer) Dept. of Pharmacology, Emory University, Atlanta, Georgia.

These studies have been conducted on unanesthetized, unrestrained rabbits with permanent intra-cranial electrodes. The EEG has been quantified with the electronic integrator of Drohocki, which continuously integrates the cortical voltage output ("electrogenesis"). This allows precise measurements of the variations in cortical electrogenesis during control periods and under the influence of drugs. Nalorphine is 3.5 times as potent as morphine in producing an increase in cortical electrogenesis. The log-dose/effect curve for morphine is a straight line between 0.3 (minimum effective dose) and 6 mg/kg. The log-dose/effect curve for nalorphine is sigmoid, the minimum significant change occurring at a dose of 0.02 mg/kg. An antagonistic effect of nalorphine on the morphine induced increase in electrogenesis manifests itself by an abrupt return to control levels. Nalorphine antagonism of morphine persists from 2 to 30 minutes depending on the ratio of nalorphine to morphine. Up to a nalorphine/morphine ratio of 0.0013 there is no antagonism; above this ratio the antagonism is complete, i.e. a return to control levels of electrogenesis. With increasing proportions of nalorphine the duration of the antagonism is prolonged. The increase of electrogenesis produced by nalorphine is not antagonized by morphine.

PLASMA PROTEIN BINDING OF RADIOACTIVELY LABELED MORPHINE, NALORPHINE AND LEVORPHANOL IN VITRO. L.B. Mellett and L.A. Woods, Dept. of Pharmacology, Univ. of Michigan Med. School, Ann Arbor.

The plasma binding of N-C^{14}-methyl morphine, H^3 labeled nalorphine and N-C^{14}-methyl levorphanol was determined in dog plasma by means of ultracentrifugation. Drug-plasma mixtures were treated according to the method of Blaney and Woods (J. Pharm. and Exper. Therap., 116: 7, 1956). The filtrates were analyzed for drug content by internal scintillation counting. Centrifugation was carried out at 7°C and at 25°C and it was observed that binding was the same for each drug at either temperature. In other experiments the binding of the drugs to plasma proteins at various pH's was determined. The pH of the plasma was adjusted by the addition of small amounts of concentrated acid or base. The protein content of plasma samples was determined spectrophotometrically using the biuret procedure. From 4 to 8 determinations were performed for each concentration and pH. The results as mean % binding are as follows. Morphine in concentrations ranging from 200 to 1000 mμg/ml, 26-27% bound. Nalorphine in concentration ranging from 600 to 1200 mμg/ml, 55-59% bound. Levorphanol in concentration ranging from 25-1000 mμg/ml, 42-44% bound. All drugs showed increased amounts of binding with increased pH; morphine 15.3% at pH 5.8 and 44% at pH 9.1, nalorphine 22.6% at pH 5.7 and 64% at pH 9.0, levorphanol 25% at pH 6.2 and 68% at pH 9.1.

Supported in part by U.S. Public Health Service Grant B-625.

PLASMA LEVELS AND URINARY EXCRETION OF TRITIUM-LABELED NALORPHINE IN DOGS. L.A. Woods and C.C. Hug, Jr.*, Dept. of Pharmacology, Univ. of Michigan Med. School, Ann Arbor.

Tritium-labeled "normorphine" was prepared following the Wilzbach procedure. The product was treated to remove chemical and radio-decomposition impurities and then reacted with allyl bromide to yield the N-allyl derivatives. The nalorphine (N-allylnormorphine) was separated from the N-allyl dihydronormorphine by-product by chromatography using thick paper buffered at pH 6.0 and the solvent system tert-amyl alcohol, n-butyl ether and water (80:7:13, v/v). Doses of 2 mg/kg of labeled nalorphine were injected subcutaneously into female dogs. Samples of plasma and urine were obtained at suitable intervals and analyzed for free and conjugated drug. Maximum plasma levels were observed for free nalorphine (0.36-0.48 μgm/ml) at 15-30 minutes after injection and for conjugated nalorphine (1.0-1.1 μgm/ml) at about 60 minutes following administration of the drug. About 5-6% of the injected drug was recovered in urine as free nalorphine and 27-40% as conjugated nalorphine. Free and conjugated nalorphine accounted for only about 50% of the total radioactivity in urine. (Supported in part by U.S. Public Health Service Grant B-625)

RELATIVE ANALGESIC POTENCY OF PHENAZOCINE AND MORPHINE. Stanley L. Wallenstein*, Ada Rogers*, and Raymond W. Houde. Sloan-Kettering Institute for Cancer Research, New York City.

On the basis of the animal pharmacology and early clinical experiences, phenazocine (NIH 7519, SKF 6574) a substituted benzomorphan, promises to be a more potent analgesic with less addiction liability than morphine. The purpose of the present study was to determine the relative analgesic effectiveness of phenazocine and morphine in patients with chronic pain due to advanced cancer. A cross-over, double blind comparison of graded doses of both medications administered intramuscularly was carried out in a series of three related sequential studies. Each patient received 8 and 16 mg. of morphine sulfate and either 1 and 2, 2 and 4 or 3 and 6 mg. of phenazocine. Pain relief scores were obtained from the patients' reports of pain severity before and at hourly intervals after receiving medication. In terms of both peak and total analgesic effects, phenazocine proved to be an effective analgesic roughly 3 to 4 times as potent as morphine. The incidence of side-effects of both drugs in these doses was small in these patients, with phenazocine showing a slight though not significant advantage.

PHARMACOLOGY AND ADDICTION LIABILITY OF DL- AND D-PROPOXYPHENE (DARVON). H. F. Fraser and Harris Isbell, NIMH Addiction Research Center, Lexington, Kentucky.

Single doses of dl ranging from 50 to 1000 mg orally, or of d-propoxyphene ranging from 50 to 650 mg orally or 5 to 60 mg subcutaneously did not induce a full pattern of morphine-like effects. When substituted for morphine for either 24 hrs. or 14 days in addicted patients both dl and d partially suppressed symptoms of abstinence from morphine but they were much less effective than codeine. Two of 5 patients who received dl chronically withdrew from the experiment; 3 patients continued after the daily dosage was reduced from 1200 to 700-850 mg daily; all patients disliked the drug because of its disagreeable side effects; 10 mg of nalorphine did not precipitate definite abstinence; following withdrawal of dl only minimal abstinence was observed. Five patients were addicted to d-propoxyphene for 53 days, and although liking the effects of the medicine initially they later developed a progressive distaste for it. After withdrawal of d, only minimal signs of abstinence were observed. Concluded that addiction liabilities of both are substantially less than that of codeine.

PHENAZOCINE (N.I.H. 7519, 'PRINADOL') AS A NARCOTIC ANALGESIC. Herbert Wendel, Irving Shemano*, and Samuel D. Ross*; Smith Kline and French Laboratories, Philadelphia, Pa.

As its chemical similarity to morphine suggests, phenazocine is also pharmacologically a morphine-like compound and possesses, besides analgesia, other activities specific for narcotics: respiratory depression, hypotension, colon spasm and constipation, excitation and mydriasis in cats, induction of tolerance, addiction liability and euphoria, and N-allylnormorphine antagonism. In equivalent doses phenazocine was about half as depressant to respiration and blood pressure (anesthetized dog), 2/3 as spasmogenic on the colon (dog), and about 1/3 as constipating (rat). Furthermore, in a crossover study none of 12 dogs vomited after phenazocine, while 40-75% had emesis after equivalent morphine doses. The same analgesic doses of both drugs protected dogs from i. v. apomorphine- and intragastric copper sulfate-induced vomiting. In rats phenazocine caused similar but somewhat slower analgesic tolerance than morphine.

Together with its reported lower addiction liability the foregoing quantitative differences indicate that phenazocine may be a better analgesic than morphine and other narcotics.

THE ANALGESIC ACTION OF DIAMPROMID AND PHENAMPROMID; N-(TERT-AMINO ALKYL)-PROPIONANILIDES. A. C. Osterberg and C. E. Rauh (intr. by W. D. Gray). Experimental Therapeutics Research, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

A series of compounds have been designed as analogs of methadon and isomethadon to retain the steric requirements of potent analgesic agents (Wright, Brabander, and Hardy, J. Am. Chem. Soc. 81: 1518, 1959). Prototypes of these are phenampromid, N-(1-methyl-2-piperidinoethyl)-propionanilide hydrochloride; and diampromid, N-(2-[(methyl)phenethylamino] propyl)-propionanilide sulfate. Analgesic activity has been assessed in mice by a modified procedure of Woolfe and Macdonald and in rats by the method of D'Amour and Smith. Diampromid was found to approximate the potency of meperidine in mice and morphine in rats. Phenampromid equalled codeine in mice and meperidine in rats. Diampromid was about twice as effective as phenampromid in elevating the response time of these animals to the heat stimuli. Both agents reduced minute volume in the unanesthetized rat, enhanced intravenous barbiturate anesthesia in mice and dogs, and inhibited gastrointestinal motility in the rat (rate of passage of a charcoal meal through the small intestine). Nalorphine effectively antagonized the analgesic and respiratory depressant actions.

OBSERVATIONS ON THE NEUROPHARMACOLOGIC EFFECTS OF PHENAZOCINE, A NEW ANALGESIC AGENT. David H. Tedeschi, Ralph E. Tedeschi and Edwin J. Fellows. Research and Development Division, Smith Kline and French Labs., Philadelphia, Pa.

Phenazocine (NIH 7519, "Prinadol") was found to be 15 to 35 times as potent as morphine as an analgesic in rats. ED_{50}'s of both compounds had similar time of onset, peak effect and duration of action. Considering its analgesic potency, phenazocine was relatively less active as a respiratory depressant in the unanesthetized rabbit in that it was only 6 times as potent as morphine. Both morphine and phenazocine produced a selective blockade of the conditioned avoidance response, phenazocine being approximately 7 times as potent as morphine. Both compounds were extremely potent antitussives in the dog (ED_{50}, s.c. = .06 and .08 mg/kg for phenazocine and morphine, respectively). Overt effects produced by morphine and phenazocine in the mouse, rat, rabbit and dog were quite similar and were, in general, characterized by catalepsy and other signs of CNS depression. Monkeys treated with phenazocine exhibited CNS stimulation, in contrast to morphine which caused characteristic depressant effects in this species.

A METHOD FOR DETERMINING MINUTE VOLUME IN UNANESTHETIZED RATS. C. E. Rauh, A. C. Osterberg, and D. T. Cote'. (intr. by W. D. Gray). Experimental Therapeutics Research, Lederle Laboratories Division, American Cyanamid Company, Pearl River, N.Y.

An apparatus has been developed which is useful in assessing the respiratory depressant effects of narcotic analgesic and hypnotic agents. Restrained, unanesthetized rats are fitted with a face mask and allowed to inspire air from a floating type spirometer through a two-way flutter valve system. Dead space must be kept at a minimum for this apparatus to function properly when respiration is severely depressed. The time required to utilize a known volume of air is determined for calculations of minute volume. Respiratory rate is observed as bubbles of air appear in a one-way water valve which also serves to counterbalance the slightly increased air pressure in the spirometer due to the weight of the float. The mean minute volume and standard deviation for 100 rats is 138.6 ± 22.8 ml./minute. The precision of this measurement is greatly increased by depressant drugs which reduce struggling efforts. Each animal serves as its own control. At subcutaneous dose levels causing a 100% increase in response time (D'Amour-Smith Analgesic Method), codeine and meperidine reduce minute volume by 50% and morphine by 60% in groups of eight rats. Nalorphine is an effective antagonist. Amounts of phenobarbital and methyprylon which cause ataxia in rats produce about a 30% reduction of minute volume.

ABSORPTION AND BRAIN UPTAKE OF HEROIN AND ITS METABOLIC PRODUCTS. E. Leong Way and Wayne A. Johnson*. Dept. of Pharmacology, University of California, San Francisco Medical Center, San Francisco, Calif.

The rate of absorption of heroin was studied by measuring its rate of disappearance from the hind leg of mice after subcutaneous administration of 37.5 mg/kg. Over 90% of the drug appeared to be absorbed within 15 minutes. The rapid disappearance of heroin was accompanied by a rapid onset in pharmacologic effects and the rapid appearance of 6-monoacetylmorphine (MAM) and morphine in the animal body. After intravenous administration of heroin 37.5 mg/kg over a 2 minute period, the brain level of heroin immediately at the end of the infusion was 6.5 μg/gm tissue and the MAM level was 21.5 μg/gm. By the next sampling period at 7.5 minutes heroin was barely detectable but the MAM level was still 16.6 μg/gm. At 30 minutes the MAM level was also barely detectable. Brain levels of morphine ranging from 2-4 μg/gm were found at 7.5, 15 and 30 minutes. Pharmacologic effects with the same dose of heroin were still evident at 120 minutes. It is concluded that in mediating pharmacologic effects heroin gains access to the central nervous system largely as MAM. During the peak of heroin action, it is probable that both MAM and morphine are eliciting pharmacologic effects but persistence of effects are mainly attributable to morphine. (Supported by National Institutes of Health, Research Grant 1839).

POTENCY DIFFERENCES OF MORPHINE-TYPE AGENTS BY RADIANT HEAT AND "CRAMPING" ANALGESIC ASSAYS PROVIDING EVIDENCE FOR A POTENTIATING SUBSTANCE FROM THE POSTERIOR PITUITARY GLAND. William J. Murray* and Jack W. Miller. Department of Pharmacology and Toxicology, University of Wisconsin Medical School, Madison.

Prior administration of the morphine-type agents prevents the "cramping" response produced by oxytocin thereby providing the basis for a quantal assay procedure. ED50 values were obtained by this procedure and by a radiant heat assay in estrogen-treated female rats. When an oxytocin-containing posterior pituitary extract was employed to produce "cramping" the ED50 values were markedly decreased relative to those obtained by the radiant heat procedure. For example, the ratio ( ) of the latter to the former ED50 values for the following agents were obtained: codeine SO_4 (2), meperidine HCl (4), dl methadone HCl (8), morphine SO_4 (14), and heroin HCl (21). However, when synthetic oxytocin was employed to produce "cramping" the ED50 values for methadone, morphine and heroin closely approximated those obtained by the radiant heat assay. The oxytocin-containing extract did not possess analgesic activity but potentiated that of morphine by the radiant heat assay; the potentiation could not be accounted for by vasopressin. Also, synthetic oxytocin did not produce potentiation. These results indicate the presence of a substance from the posterior pituitary gland which potentiates the analgesic activity of morphine-type agents in proportion to their relative potencies. (Supported by a grant from the Wisconsin Alumni Research Foundation)

CHEMOTHERAPY AND ENDOCRINOLOGY

Room N-205, Memorial Building

CHEMICAL MEASUREMENT OF MITOMYCIN C IN BODY FLUIDS AND TISSUES. M. Freeman Narrod. The Children's Cancer Research Foundation, and Dept. of Pharmacology, Harvard Med. School, Boston, Mass.

The spectroscopic properties of Mitomycin C, a new anti-tumor agent, have been examined and adapted for use in measuring its concentration in body fluids and tissues. The compound is extracted from a concentrated salt solution with butanol. Its optical density at 363 mμ is measured before and after the addition of acid. This change in optical density is proportional to the concentration of drug present. Using these properties, studies have been made of the disposition of mitomycin by the mouse. Twelve hours after the intraperitoneal administration of a single dose, approximately 20% remained in the body. No detectable amounts were found in the feces. Approximately 20% was excreted in the urine and the remaining 60% was thought to be metabolized or broken down in the body.

METABOLISM AND EXCRETION OF MITOMYCIN C BY RATS. Herbert S. Schwartz*, Alice P. Cronin*, and Frederick S. Philips. Sloan-Kettering Institute for Cancer Research, New York, New York.

The mitomycins are a group of antibiotics isolated by Hata et al. (1956) from Streptomyces caespitosus. In particular, mitomycin C is of interest because it inhibits growth of a relatively large number of rodent tumors (Sugiura, 1959). Quantitative measurement depends upon ultraviolet absorption at 363 mμ or bioassay (inhibiting growth of B. subtilis plated on agar with minimal media). Administered intravenously to rats, mitomycin C disappears rapidly from the plasma. Urinary excretion also is initially rapid. After large intravenous doses (e.g., 8 mg/kg or 4 x LD_{50}), only 30% of the amount administered can be recovered in the urine. At doses closer to the LD_{50}, e.g., 2 mg/kg, total recovery is 18%. The rapid disappearance of mitomycin from the plasma can be slowed slightly by nephrectomy. Animals whose livers were damaged by treatment with CCl_4 48 hours prior to administration of mitomycin C excreted only slightly more of the drug than did controls. Tissue degradation of mitomycin C can be demonstrated with liver homogenate incubated in phosphate-buffered saline (pH 7.4) under nitrogen. The destruction is sufficiently rapid to account for the in vivo disappearance of mitomycin C from the blood after nephrectomy as well as low urinary recoveries after CCl_4.

TREATMENT OF CARCINOMA WITH CYANIDE AND ANESTHESIA. A.M. Smith, J.E. Stone, and C.D. Wood, (intr. by Lloyd D. Seager). Dept. of Pharmacology, Univ. of Arkansas Medical Center, Little Rock, Ark.

A selective toxicity for Ehrlichs Ascites tumor by cyanide and ether combinations has been reported by these authors (Proc.Soc. in press). These data represent an extension of that work. Groups of 20 gm. male Swiss mice were injected intraperitoneally with Ehrlichs or Sarcoma 180 ascites tumors ($4X10^6$ cell count). Treatment of .75 mg/kg cyanide (I.P.) with anesthesia was given 48 hours later. Average survival times were compared between treated and control animals. An increase of survival time of 70% was found for the treated animals of both groups. A group of dogs with spontaneous tumors were treated with I.V. cyanide (.75 mg/kg) while under anesthesia. Five of the six dogs so treated showed a marked improvement in their condition histologically as well as grossly. Two dogs with cataracts of the eye showed marked improvement in this condition. These drugs appear to act by blocking the oxidative metabolism of the cancer cells which as Warburg suggests may be at an irreducible minimum. This drug combination appears to have a significant therapeutic index for malignant tumors.

THE RELATION BETWEEN THE BINDING OF SULFONAMIDES TO ALBUMIN AND THEIR CHEMOTHERAPEUTIC EFFICACY. A.H.Anton (intr.by T. H. Haren). Department of Pharmacology and Therapeutics, University of Florida College of Medicine, Gainesville.

Direct evidence is presented that the albumin-bound fraction of sulfonamides is chemotherapeutically inert. Dialysis bags ("intravascular compartment") containing 3% bovine albumin in 3 ml. of medium, or medium alone; were suspended in 10 ml. of the same medium containing serial dilutions of a sulfonamide ("extravascular compartment"). Inoculation of E.coli/B into either compartment gave similar results since growth inhibition was found related to conc. of free drug. With sulfaethylthiadiazole (98% bound at the conc. used) there was 50% growth inhibition at 2.8 μg/ml without albumin (free drug) and 36 μg/ml with albumin present (bound+free). However, with sulfadiazine (40% bound) 50% inhibition was caused by 1.4 μg/ml free and 1.7 μg/ml. total drug. No correlation was obtained between binding and antibacterial potency of a sulfonamide.

Increasing the free fraction of sulfonamide by using larger amounts against a resistant organism, or by displacement from bound sites by another drug, overcame the interference of albumin. Thus, although binding interferes with antibacterial action in vitro at low conc. (< 5 μg/ml) these data also show that at conc. required in vivo (100 μg/ml) interference caused by binding is probably negligible.

ON THE BINDING OF AROMATIC SULFONAMIDES TO ERYTHROCYTES. Thomas H. Maren, Bettie Robinson* and Roger F. Palmer*. Department of Pharmacology and Therapeutics, University of Florida College of Medicine, Gainesville.

Earlier in vivo work showing that sulfanilamide (S) and acetazolamide (A) had an affinity for mammalian rbc was confirmed and extended. 14 sulfonamides were studied in vitro. Ten unsubstituted drugs (Aryl-SO_2NH_2), all carbonic anhydrase (C.A.) inhibitors, had varying degrees of affinity to rbc. Four substituted drugs (Aryl-SO_2NHR), all antibacterial agents, had no such affinity. Both S and A accumulated in rbc to about 70 μM/L, against concentration gradients. S and other benzenesulfonamides could be washed out, but A and other heterocycles could not. $K_{diss.}$ of S-rbc is 10^{-6}M; that of A-rbc is $<10^{-12}$M. A interferes competitively with accumulation of S in rbc. Formation of A-rbc is not dependent on energy, or pH, or temp. Rbc of bird, reptile and fish also bind A. Binding is to a component within cell, probably not hemoglobin or C.A. A has no affinity to other tissues containing C.A., such as lens. However, the drug receptor in red cells has a "fit" similar to C.A. since both react quite specifically with Aryl-SO_2NH_2. Apart from the bound moiety, A exists both in vivo and in vitro in diffusible form in red cells. This is in rapidly attained equilibrium with unbound unionized drug in plasma. Drug bound to rbc appears inactive against C.A., but the diffusible component inhibits C.A. in rbc and leads to venous and tissue retention of CO_2.

SIMILARITIES BETWEEN SOME PHARMACOLOGICAL EFFECTS OF METHYL-GLYOXAL-BIS-GUANYLHYDRAZONE (CH_3-G) AND OF DECAMETHYLENE-DIGUANIDINE (SYNTHALIN). E. Mihich and A.I. Mulhern*. Dept. of Exper. Therapeutics, Roswell Park Memorial Inst., Buffalo, N.Y.

The inhibitory effects of CH_3-G in Leukemia L1210 (Freedlander and French, Cancer Research 18:360-63, 1958) have been confirmed by others and by ourselves. During preclinical pharmacological studies of CH_3-G (Mihich et al., Proc. Am. Assoc. Cancer Research 3:43, 1959) it was noticed that in dogs the delayed death which occurred after single i.v. injection of 50 mg/Kg of CH_3-G, was preceded by generalized convulsions which could be reversed by glucose. Further experiments revealed that CH_3-G caused delayed hypoglycemia in rabbits and potentiation of both the convulsive and the lethal effects of insulin in rats. These results suggested a study of the antitumor effects of Synthalin. Growth of ascitic Sarcoma 180 and Leukemia L1210 in mice treated i.p. with Synthalin (2 to 8 mg/Kg/day for 7 days) was strikingly impaired (maximum inhibition 99% - cell counts). The effects of some other hypoglycemic agents, not containing the diguanidine moiety, were tested on ascitic Sarcoma 180. Preliminary data indicated that Tolbutamide, Chlorpropamide and Metahexamide were ineffective and that Phenformin (a monoguanidine derivative) was moderately active. The possibility that the antitumor activity of CH_3-G and Synthalin is related to the hypoglycemic effects of these compounds thus seems unlikely.

PHARMACOLOGY OF 5-MERCAPTOURACIL, (5 MU), 2,4 DIAMINO-6,7-DIMETHYL-2,4 DEOXYALLOXAZINE (DA), BIS(ETHYLENEMIDO) PHOSPHOROURETHAN (EPO) AND ITS BENZYL ANALOG (BPO). Julian L. Ambrus, Clara M. Ambrus, Nathan Back, Leon Stutzman*, Joseph E. Sokal,* and Charles A. Ross*. Roswell Park Mem. Inst. and Dept. of Pharmacology, Univ. of Buffalo School of Med.

Synthesis and preliminary screening for chemotherapeutic activity of these compounds has been reported previously (Bardos, Papanastassiou, Ambrus, Segaloff, Weeth: J. Am. Chem. Soc. 77, 960, 1955; 78, 401, 1956; 79, 4704, 1957; Nature 183, 399, 612, 1959; Proc. Cancer Res. 3, 2, 62, 1959). In microbiologic systems DA was found to be a folinic acid (but not folic acid) and riboflavin antagonist; 5 MU blocked thymidine synthesis; EPO and BPO behaved as alkylating agents. DA, EPO and BPO inhibited a series of transplanted and spontaneous mouse and rat tumors. 5 MU was ineffective alone but potentiated the effect of DA, 5-fluorouracil, 5-flurodeoxyuridine and folic acid antagonists. The compounds were tested for acute and subacute toxicity in mice, rats, dogs, and monkeys and for various pharmacologic effects in dogs and monkeys. EPO and BPO produced bone marrow depression and hemorrhagic enteritis similar to nitrogen mustard, but caused less emesis in dogs; they exhibited analgesic and some ataraxic effect. In clinical-pharmacologic studies inoperable patients, resistant to other chemotherapeutic agents were studied as well as cases where tissue cultures of tumor biopsies showed greater sensitivity in vitro to these agents than to established chemotherapeutic drugs.

THE ANTI-INFLAMMATORY ACTIVITY OF FOUR LICORICE EXTRACTS. R. J. Girerd*, G. Di Pasquale* and C. C. Scott. Warner-Lambert Research Institute, Morris Plains, N. J.

Ammoniated glycyrrhizin (1), alpha glycyrrhetinic acid (2), beta glycyrrhetinic acid (3) and a fraction (4) containing the alpha and beta isomers (Licrysone), were tested for their anti-inflammatory properties by the cotton pellet method in normal and adrenalectomized rats. Results were expressed as percentage of inhibition of granuloma formation after 11 days of daily treatment. In the normal rat high subcutaneous doses (500 mg/Kg/day) gave the following results: 46%(1), 26%(2), 38%(3) and 39%(4); after adrenalectomy and maintenance on 0.87% saline, a similar order of activity was found: 40%(2 and 3) and 38%(4), while ammoniated glycyrrhizin was toxic. No satisfactory dose-response relationship could be established. Large oral doses (500 mg/Kg/day) were totally ineffective. When incorporated in each of the two cotton pellets, at the dose of 5 mg, none of the insoluble compounds tested (2, 3 and 4) were found active. It is concluded that licorice extracts have an intrinsic, but very weak, anti-inflammatory effect, apparently due to glycyrrhetinic acid. The activity is approximately 1/50 that of cortisone acetate.

PLASMA LEVELS OF 17-HYDROXYCORTICOSTEROIDS DURING ETHANOL INTOXICATION IN DOGS. Fred W. Ellis. Dept. of Pharmacology, University of North Carolina School of Medicine, Chapel Hill, N. C.

In the course of investigations designed to study the relationship between experimental alcoholism and adrenocortical function, plasma concentrations of 17-hydroxycorticosteroids in dogs were determined following the intravenous administration of ethyl alcohol. Venous blood samples for ethanol and steroid analyses were taken prior to the injection and at certain intervals of time thereafter. The animals received alcohol in doses of 1, 2 and 3 gm./kgm. In control experiments in which ACTH was injected the anticipated significant rise in steroid concentration was observed. When saline alone was given, insignificant increments in plasma level occurred. Ethanol intoxication was accompanied by notable increases in plasma-steroid concentration which could be correlated with the alcohol content of the blood. The steroid response to the largest dose of alcohol was similar in magnitude to that elicited by 1.2 units/kgm. of ACTH.

SELECTED STUDIES RELATING TO THE CHEMISTRY OF THE INFLAMMATORY SITE. Leonard B. Achor, William Bowers*, and Raymond F. Geoffroy*. The Merck Institute for Therapeutic Research, Rahway, N. J.

In a previous communication (Fed. Proc. 18: 362, 1959), a procedure for the production of granulation (inflammatory) tissue in useful quantities was described. The availability of such "pathological" material from the SAS Granuloma Pouch has permitted preliminary study of biochemical changes incident to the inflammatory state. Data pertinent to the following aspects of this problem will be presented: (1) incorporation of hexosamines and N-acetyl analogues into di- and oligosaccharides, (2) enzymatic activity associated with the hydrolysis of disaccharide substrates and (3) the ability of granulation tissue preparations to hydrolyze (in vitro) synthetic di- and tri-peptides, including triglycine, diglycine, glycyl-L-leucine, and glycyl-L-proline. In addition, information relative to modification of (the above) reaction rates by steroid and non-steroid anti-inflammatory agents will be discussed.

CORTICOTROPIN RELEASE FOLLOWING THIRD VENTRICLE INJECTION OF MINUTE DOSES OF VASOPRESSIN. H.C. Kwaan and H.J. Bartelstone. (intr. by H.B. van Dyke). Dept. of Pharmacology, College of Physicians and Surgeons, Columbia Univ., New York, N.Y.

Trained, female, mongrel dogs, weighing 10-14 kg., were prepared with third ventricle cannulae according to the technique of Bartelstone et al. (J. App. Physiol., 13, 142, 1958). Adrenal vein blood was collected and 17-hydroxycorticosteroid secretion estimated according to the technique and analytical procedure of Hume and Nelson (Surg. Forum, 5, 568, 1955). Injections were made in conscious dogs 24-48 hours after cannulae were implanted. Pain from the adrenal vein occlusion site was eliminated by the infiltration of 2% procaine hydrochloride. Resting adrenal 17-hydroxycorticosteroid secretion ranged between 1.5 to 2.5 µgm. per minute. After third ventricle injection of 2 mU of arginine vasopressin in 0.25 ml. of van Dyke-Hastings solution, pH 7.2, adrenal 17-hydroxycorticosteroid secretion rose to a peak of 7.3-17.0 µgm. per minute in 11 to 16 minutes. Injections of 0.25 ml. of the vehicle alone or with 2 mU oxytocin were alternated with the vasopressin injections. There was no significant increase in adrenal 17-hydroxycorticosteroid secretion in these controls. The results demonstrate that a minute dose of vasopressin, injected into the third ventricle, can cause the release of corticotropin in the dog. (Supported by U.S.P.H.S. grant H 1788).

TESTOSTERONE INHIBITION OF OVULATION IN HEIFERS. Hugo Krueger and Ralph Bogart*. Dairy and Animal Husbandry, Oregon State College, Corvallis, Oregon.

Testosterone treated heifers generally did not ovulate as evidenced by lack of corpora lutea when slaughtered. In 24 heifers treated with testosterone, only 16 per cent had ovulated at a weight of 800 lbs. whereas 100% of the 24 control heifers had ovulated. Testosterone had been administered in micropellets intramuscularly at the rate of 1.0 mg per kg weekly from weaning (around 450 pounds) onward. Two additional heifers, injected with testosterone, showed no heat cycles. However, 30 days following cessation of testosterone treatment, these heifers bred and conceived. Testosterone injections yield an increased daily rate of gain of 0.2 lb. in steers and 0.5 lb. in heifers and a decreased feed requirement per 100 lb. gain in steers of 41 lbs. and in heifers of 180 lbs. with no change in daily feed intake. Control heifers gained 2.0 lbs. and control steers 2.5 lbs. daily. Testosterone caused a marked increase in protein content and a marked decrease in the fat content of the carcass. Both heifers and steers receiving testosterone developed marked crests in the neck region. Other signs of masculinization included sweating, alteration of hair coat, and deepening of sound in bellowing. Masculinization did not interfere with palatability or tenderness of the meat. (Oregon Agricultural Experiment Station Bulletin 31)

MONOAMINE OXIDASE INHIBITORS

Beaumont Lecture Hall, Memorial Building

ON THE ENZYMIC SPECIFICITY OF ANTI-DEPRESSANT MONOAMINE OXIDASE (MAO) INHIBITORS. I. I. A. Tabachnick. Dept. of Pharmacology, Scientific Research Div., Schering Corp., Bloomfield, N. J.

It has been postulated that anti-depressant compounds such as JB-516 (I), iproniazid (II), and nialamide (III) exert their therapeutic effects by inhibiting MAO. These compounds, however, are inhibitors of many enzyme systems and it appeared of interest, therefore, to ascertain their relative efficacy as inhibitors of other enzymes. The following enzymes were studied: MAO obtained from guinea pig liver, rabbit liver, and mouse brain employing nor-epinephrine, 5-hydroxytryptamine, and tyramine as substrates; diamine oxidases (DAO) obtained from porcine kidney and rabbit liver employing putrescine and mescaline, respectively, as substrates; DOPA decarboxylase of rat and guinea pig kidney; glutamic acid decarboxylase of guinea pig brain. I showed consistant potency as an MAO inhibitor regardless of the enzyme source or substrate (pI_{50} = 5.6-5.9). The potency of II and III, however, varied depending on the MAO source or substrate. The order of potency as MAO inhibitors in all cases was I > III > II. Employing hog kidney DAO, order of potency (with pI_{50}) was I (4.4) > II (3.7) > III (2.9). Harmine was relatively weak as a DAO inhibitor. I, II, III were almost equal in activity as inhibitors of the oxidation of mescaline by rabbit liver. Decarboxylase studies indicated that I, II, and III were relatively weak.

LIMITING FACTORS IN MONOAMINE OXIDASE (MAO) INHIBITION. M. I. Gluckman and Zola Horovitz* Vet. Admin. Res. Labs. in Neuropsychiatry & Dept. of Pharmacology, Univ. of Pittsburgh, Pittsburgh, Pa.

This study compares the MAO inhibitory properties of iproniazid (I) and phenylisopropylhydrazine (JB-516) (II) and tissue factors involved in limiting this inhibition. A method using phosphomolybdic acid was developed for the determination of the hydrazine inhibitors. Rat brain slices are incubated with 6 cc. of 4×10^{-4} molar I or II. At different time intervals an aliquot of fluid is removed and the hydrazine concentration determined. In 30 min. uptake is almost complete for both I and II; approximately 17% and 46% respectively. Only a small further increase in uptake takes place in 2 hours. Although with I uptake is almost maximal in 30 min., there appears to be a continuous increase in MAO inhibition over the entire 2 hour period. With II the MAO inhibition closely follows uptake. In contrast to slices, mitochondria do not concentrate the inhibitors suggesting a simple diffusion process. This evidence indicates not only an inherent difference in the degree and development of the inhibitory action of I and II but also a difference determined by the ability of the inhibitors to penetrate.

RELATIVE ACTIVITIES OF TWO PARTICULATE ENZYMES, MONOAMINE OXIDASE AND SUCCINOXIDASE, IN VARIOUS PARTS OF BRAIN. Norman Weiner, Dept. of Pharmacology, Harvard Med. School, Boston, Mass., intr. by O. Krayer.

Bogdanski and Udenfriend (J. Pharmacol. 116: 7, 1956) demonstrated the nonuniform distribution of monoamine oxidase (MO) in dog brain. It seemed pertinent to extend these findings by relating the activities of MO to another mitochondrial enzyme system; e.g., succinoxidase (SO), in various parts of the brain. Highest activity of MO has been found in the hypothalamic, thalamic, and corpus callosal regions. Lowest activities were found in the white matter of the cortex and in the cerebellum. The grey matter of the cortex and the medulla-pons regions were intermediate in MO activity. SO activity was found to be highest in grey matter of cerebral cortex and in cerebellum, and lowest in white matter of cortex and medulla-pons region. Similar relative activities of the two enzymes were found for both homogenates and mitochondrial preparations. The similar partition of enzymes by differential centrifugation suggests these enzymes are predominantly or exclusively in the same particles; i.e., those with sedimentation characteristics of mitochondria. The varying ratio of activity of SO/MO in different parts of the brain is further evidence for the heterogeneity of these particles. (Supported by USAF Sch. Av. Med. Contract AF 41 (657)-197 (7756-132).

DEPRESSANT ACTION OF JB-516 (CATRON) ON PERIPHERAL NERVE. G.A. Condouris (intr. by D.D. Bonnycastle). Dept. of Pharmacology, Seton Hall College of Medicine & Dentistry, Jersey City 4, N.J.

JB-516 depresses nerve excitability in concentrations greater than .001 M. Concentrations around .001 M. block in 30 to 60 minutes; .010 M. blocks all fibers in 10 minutes or less. Superficially, the block resembles that obtained with cocaine or procaine. In several respects, the action of JB-516 differs from the effects of the two classical local anesthetics. Reversal of the block, by application of drug-free Tyrode solution, is exceedingly difficult. Conduction can be restored in about half of the fibers. However, a secondary irreversible block develops subsequently in the absence of externally applied JB-516. The depression of excitability with JB-516 develops with minimal effect on the conduction velocity, and finally, the nerve is still able to conduct trains of impulses while the excitability undergoes depression. JB-516 is approximately 1/2 as potent as procaine and 1/10 as active as cocaine.

MONOAMINE OXIDASE INHIBITORS AND NEUROMYAL BLOCK. Edmund G. Anderson, (intr. by D.D. Bonnycastle). Dept. Pharmacol., Seton Hall Col. of Med., Jersey City, New Jersey.

Gertner's recent report (Nature 183:750,1959) that several monoamine oxidase (MAO) inhibitors blocked transmission in the sup. cerv. ganglion raises the possibility of these inhibitors acting elsewhere on the peripheral nervous system. Several MAO inhibitors were tested for blocking activity at the neuromyal junction. Using the isolated frog sartorius muscle-sciatic nerve preparation, it was found that harmine produced complete blockade of neuromyal transmission in concentrations of 1.6×10^{-4} M. Iproniazid and phenyl isopropylhydrazine blocked transmission in 1.6×10^{-3} and 6×10^{-4} M. concentrations respectively. Isoniazid failed to block in concentrations as high as 3.3×10^{-3} M. In all cases the muscle response to direct stimulation remained unaltered, and the block was rapidly reversed when the drug was washed out within 15 minutes of application.

SOME PHARMACOLOGIC ACTIONS OF IPRONIAZID ON ISOLATED ATRIA OF THE GUINEA PIG. S. Schanberg*, G. Pepeu*, and N. J. Giarman, Dept. of Pharmacology, Yale Medical School, New Haven, Connecticut.

In order to elucidate any relationship between activity of monoamine oxidase (level of endogenous catechol- and other amines) and cardiac activity, a study of some of the pharmacological actions of an inhibitor of monoamine oxidase, iproniazid (Marsilid), on isolated guinea pig's atria was undertaken. Iproniazid and a methylated derivative (WY-572) increased rate and contractility without changing characteristics of the electrogram. This stimulation reached a maximum in one hour and persisted for several hours; but it was completely inhibited by non-toxic levels of the sympatholytic compound, dichloro-isoproterenol (DCI). By contrast, isoniazid had no stimulatory effect in doses equi-molecular to those of iproniazid. Reserpine, in a concentration of 10γ/ml., produces arrhythmia and an increasing negative inotropic and chronotropic effect, leading to stand-still in six to seven hours. Atria in reserpine-induced stand-still can be re-started by a number of catecholamines (e.g., epinephrine). It was found that iproniazid in various doses, WY-572, and isoniazid, when administered repeatedly during two hours prior to reserpine, antagonized the reserpine-induced depression, but to a varying extent, shown to be correlated with the degree of inhibition of monoamine oxidase.

OBSERVATIONS ON THE CARDIOVASCULAR PHARMACOLOGY OF NIALAMIDE AND CERTAIN OTHER MONOAMINE OXIDASE INHIBITORS. Murray Finkelstein, Violet N. Niesler and Clara M. Kromer (intr. by Jurg A. Schneider). Dept. of Macrobiology, Research Division, Chas. Pfizer and Co., Inc., Groton, Conn.

The equivalent of human therapeutic doses of nialamide, 1-[2-(benzylcarbamyl)ethyl]-2-isonicotinoyl hydrazine, was essentially devoid of cardiovascular activity in animal experiments and only in relatively high intravenous doses were changes observed. This is similar to certain other monoamine oxidase inhibitors but in contrast to those that are active in low doses and which possess sympathomimetic activity. Because of the orthostatic hypotension frequently seen in man receiving this class of compounds, and in order to assess the integrity of compensatory mechanisms in their presence, experimental procedures were designed in which arterial blood pressure of dogs and cats was measured while their postural attitude was altered 90 degrees from a horizontal to a vertical position. Unlike results obtained with some agents, orthostatic hypotension was not observed in dogs following either acute intravenously or chronic orally administered nialamide. These comparative results and other cardiovascular studies in dogs and cats will be discussed.

IN VIVO INHIBITION OF MONOAMINEOXIDASE BY 2-PHENYLCYCLOPROPYL AMINE (SKF385). Erminio Costa, Galesburg State Research Hospital, Galesburg, Illinois.

0.011 to 0.024 mM/kg of SKF trans 385 caused a three to fourfold increase of brain serotonin content of mice, rats, rabbits and dogs. Maximal effects were obtained within 6 hrs; 30 to 40 hrs. thereafter serotonin contents are normal. In mice the effects of 5 HTP on brain serotonin concentration were potentiated by 0.029 mM/kg of SKF trans 385. In rats SKF cis 385 is less active than the trans isomer; 0.021 mM/kg of amphetamine failed to modify brain serotonin content. The serotonin increases found in brain of rats after 0.014 mM/kg of SKF trans 385 were at any time proportionally greater than those of spleen, intestine, lung and kidney. 0.135 mM/kg of iproniazid or 0.020 mM/kg of SKF trans 385 in 6 doses during 60 hours caused a 350% increase of brain serotonin of rats. In similar experiments 5 mg/kg of reserpine were given after 24 hours of pretreatment: 0.010 mM/kg of SKF trans 385 or 0.135 mM/kg of iproniazid counteracted reserpine effects on brain serotonin; both drugs failed to antagonize the effects of reserpine on spleen serotonin content. 0.007 mM/kg of SKF trans 385 given 1 hr. after 2.5 mg/kg of reserpine counteracted brain serotonin depletion.

EFFECT OF β-PHENYLETHYLHYDRAZINE AND RELATED COMPOUNDS ON RESPONSE OF RABBIT AORTIC STRIPS TO SYMPATHOMIMETIC AMINES. Jonas A. Gylys*, Max Chessin* and M. R. Warren. Warner-Lambert Research Institute, Morris Plains, New Jersey.

β-Phenylethylhydrazine (I) has been shown to be a potent, rapidly-acting monoamine oxidase inhibitor with long duration of action (Chessin, et al, in press). 5γ of (I) per ml. of bath solution potentiated the motor responses of aortic strips to l-norepinephrine and l-epinephrine but the effect was readily reversible by washing of the tissue. Phenylethylamine, an amine homolog of (I), did not show any potentiating effect. The contractile responses to tyramine and cobefrine (α-methyl-dl-norepinephrine) likewise were potentiated by (I); cobefrine is not metabolized by monoamine oxidase. Comparative studies with hydrazine derivatives related to (I) showed no direct correlation between the effects on aortic strips and blood pressure responses in anesthetized dogs. Data will be presented to show that potentiation of epinephrine and norepinephrine responses of aortic strips by β-phenylethylhydrazine is probably not related to monoamine oxidase inhibition.

CARDIOVASCULAR ACTIVITY OF β-PHENYLETHYLHYDRAZINE (PHENELZINE). Max Ben*, Marshall R. Warren, Virginia P. Drinnon* and Charles C. Scott. Warner-Lambert Research Institute, Morris Plains, New Jersey.

β-Phenylethylhydrazine (phenelzine) has been demonstrated by biochemical and pharmacological studies to be a potent monoamine oxidase inhibitor. Reports in the literature have indicated that certain monoamine oxidase inhibitors are useful for the treatment of angina pectoris. The mechanism of action of these agents in this condition has not been elucidated. Studies in anesthetized dogs demonstrate that phenelzine is a coronary artery dilator. Results will be reported concerning the effect of this substance on the rate of coronary blood flow, cardiac contractile force and cardiac output. Comparison of the responses to serotonin, epinephrine and norepinephrine before and after the administration of phenelzine will be discussed.

LACK OF CORRELATION BETWEEN EXCITEMENT AND BRAIN AMINE CONTENT AFTER MONOAMINE OXIDASE INHIBITORS AND AMINE PRECURSORS IN RATS.
S.M. Hess, W. Doepfner*, and S. Udenfriend. National Heart Institute, Bethesda, Md.

Rats pretreated with monoamine oxidase inhibitors (MAO-I) followed by tryptophan (TPH) (200-800 mg/kg) or 5-hydroxytryptophan (5HTP) (5-120 mg/kg) exhibited in certain cases characteristic excitement. To learn if indoleamines were directly responsible for this phenomenon rats pretreated with marsilid, JB-516, or Nialamid during various time intervals were given TPH or 5HTP. After treatment animals were observed up to two hours, then brains and livers assayed for serotonin and tryptamine. Levels of serotonin and tryptamine in the experimental animals were in no way directly related to the excitement produced. Animals with no symptoms could be produced with amine levels comparable to others with marked symptoms. Lack of correlation between excitement and serotonin level was found to be no better even when specific parts of the brain were assayed. MAO-I alone and TPH alone are incapable of producing excitement. 5HTP can produce the first stage of excitement only after a massive dose (320 mg/kg). It is apparent that the increase of brain indoleamines is not in itself sufficient to produce excitement. The requirements are an amine precursor and a MAO-I, which suggests the excitement is caused by an altered route of metabolism of the precursor or to a sensitization to the action of the amine products by the MAO-I.

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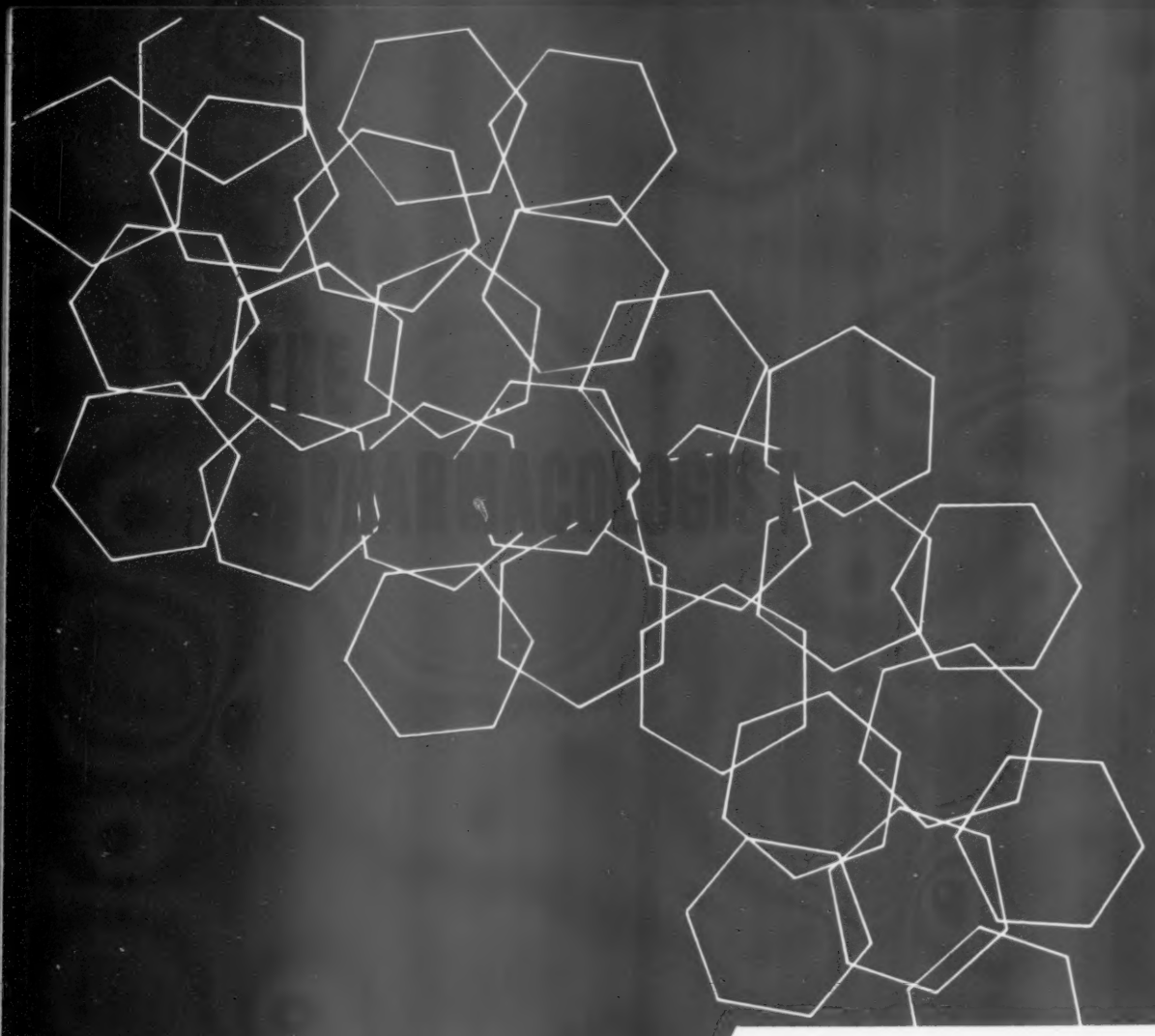

This Issue Contains Abstracts Of Papers To Be Presented At The Miami Meeting Of The Society, Aug. 31 - Sept. 3, 1959